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Review Article

Preeclampsia: An Overview

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Abstract

Preeclampsia is one of the leading causes of maternal morbidity/mortality and represents one diagnosis on a continuum of hypertensive disorders affecting pregnancy. The proposed two-fold etiology includes abnormal placentation and systemic maternal endothelial dysfunction. Multiple risk factors have been identified to aid in anticipating this disease, including preeclampsia in a prior pregnancy. Timely diagnosis and management may have a significant impact on both maternal and fetal outcomes.

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INTRODUCTION

Preeclampsia is encountered worldwide, complicating five to eight percent of all pregnancies [1]. It is one of the leading causes of maternal and fetal morbidity and mortality. It is vital that providers who care for pregnant women are familiar with this relatively common pregnancy-related disease. Definition, diagnosis, pathogenesis, clinical presentation, and management of preeclampsia will be discussed.

Definition and diagnosis

There is a spectrum of hypertensive disorders that affect pregnancy as outlined below.

Preeclampsia: Preeclampsia is defined as hypertension plus proteinuria. This diagnosis is most commonly made after 20 weeks gestational age and may also be diagnosed in the postpartum period.

Hypertension is defined as blood pressure recordings of greater than 140 mmHg systolic, greater than 90 mmHg diastolic, or both.

Proteinuria is defined as 300 mg or more of protein in a 24-hour urine collection or a protein: creatinine ratio of 0.3 mg/dL using a spot urine protein and spot urine creatinine.

Preeclampsia is further subdivided based upon the severity of disease. The term "preeclampsia without severe features" is defined as hypertension with proteinuria (formerly, readers may have seen this diagnosis as "mild preeclampsia").

The term "preeclampsia with severe features" has been recently re-defined as blood pressures of greater than 160 mmHg systolic, greater than 110 mmHg diastolic, or both plus evidence of end organ dysfunction (Table 1). It is important to note that the diagnosis of "preeclampsia with severe features" is no longer contingent on the presence of proteinuria as long as the diagnosis can be made with severe range blood pressures plus one other additional severe feature signifying end organ damage.

Eclampsia: Defined as the convulsive phase of preeclampsia, signified by generalized tonic-clonic seizure activity. It is commonly preceded by premonitory events such as a severe headache, hyperreflexia, blurred vision, photophobia, epigastric or right upper quadrant pain, or altered mental status. However, eclampsia may occur in the absence of any warning signs or symptoms.

Gestational hypertension: Defined as blood pressure elevation after 20 weeks gestational age without proteinuria or laboratory abnormalities. Gestational hypertension complicates approximately 6% of all pregnancies. Approximately 15-25% of patients with gestational hypertension will ultimately develop preeclampsia. If blood pressures fail to normalize in the postpartum period, the diagnosis is changed to chronic hypertension.

Chronic hypertension: Defined as blood pressure elevation that predates pregnancy, hypertension diagnosed before 20 weeks gestational age, or blood pressure that remains elevated six weeks postpartum. Chronic hypertension complicates 3-5% of all pregnancies.

HELLP syndrome: Defined as a collection of laboratory abnormalities (Hemolysis, Elevated Liver enzymes, and Low Platelets). Notably, this diagnosis can be made in the absence of blood pressure abnormalities. Although the relationship between

Table 1: End Organ Dysfunction in Preeclampsia.

Thrombocytopenia	Platelet count < 100, 000/microliter
Liver dysfunction	AST or ALT > 2x upper limit of normal
Renal insufficiency	Creatinine > 1.1 mg/dL or doubling of baseline creatinine
Pulmonary edema	
Central nervous system disturbances	Headache, scotomata, blurred vision, altered mental status

HELLP syndrome and preeclampsia remains unclear, this diagnosis is considered to be a subtype of preeclampsia. HELLP syndrome may be seen in 0.1-0.8% of all pregnancies and in 10-20% of pregnancies ultimately complicated by preeclampsia with severe features.

Pathogenesis

As described by Lain and Roberts [2], preeclampsia is thought to be a two-stage disease.

First stage: The first stage is abnormal placentation. Because it is the placenta (and not the presence of a fetus) that initiates the disease process, preeclampsia may be seen in hydatidiform molar pregnancies. Normally, cytotrophoblast cells from the placenta remodel maternal spiral arteries, transforming them from small, muscular arterioles into large diameter arteries with high capacitance. Remodeling typically begins in the late first trimester and is completed by 18-20 weeks gestation. Failure of complete remodeling results in decreased placental perfusion, which alters maternal endothelial cell function.

Second stage: The second stage of preeclampsia is a systemic disorder characterized by endothelial dysfunction in the maternal circulatory system. Although the exact mechanism remains unknown, it is thought that several factors contribute to this dysfunction: increase in systemic anti-angiogenic factors, activation of an inflammatory response, and presence of certain immunologic factors. As a result of systemic endothelial dysfunction, preeclampsia manifests in signs and symptoms that reflect maternal multi-organ damage outlined in (Table 1).

Risk Factors

There are several well-studied risk factors for preeclampsia (Table 2). The magnitude of risk is dependent on the individual risk factor, severity, and the number of risk factors. The greatest risk may be seen in patients with maternal antiphospholipid antibody syndrome (a nine-fold increased risk for developing preeclampsia) followed by patients with a history of preeclampsia in a prior pregnancy (a seven-fold increased risk) [3]. Specifically, increased severity of preeclampsia in prior pregnancy is associated with a higher risk for preeclampsia in subsequent gestation.

Maternal Outcomes

Eclampsia is associated with a high risk of maternal morbidity and mortality. Eclampsia complicates 2-3% of women diagnosed with preeclampsia with severe features who are not receiving anti-seizure prophylaxis (magnesium sulfate) and up to 0.6% of women diagnosed with preeclampsia without severe features [4]. Significant maternal sequelae include intracerebral hemorrhage, transient blindness, and cardiorespiratory arrest. Permanent neurologic damage from brain ischemia or hemorrhage is the most common causes of maternal death, with the maternal mortality rate ranging from 0-14% [5].

Recurrence Risk

In regards to the recurrence of preeclampsia, a meta-analysis by van Ostwald et al. [6], found that approximately 20% of women with preeclampsia will develop pregnancy-related hypertension and 16% will be diagnosed with preeclampsia in subsequent pregnancies. For patients with eclampsia in a prior pregnancy, the recurrence risk in a subsequent pregnancy appears to be about 2%, with the risk decreased in the setting of timely diagnosis and administration of magnesium for seizure prophylaxis [7].

Table 2: Risk Factors for Preeclampsia.

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Prior pregnancy with preeclampsia
Chronic hypertension
Chronic renal disease
History of thrombophilia
Multiple gestation pregnancy
In vitro fertilization
Family history of preeclampsia
Type I or Type II diabetes mellitus
Obesity
Lupus
Age > 40
Prolonged pregnancy interval
Black race
Hydatidiform mole

Future Risk of Cardiovascular Disease

Preeclampsia and pregnancy-related hypertensive disorders have been recognized by the American Heart Association as major risk factors for the development of future cardiovascular disease including myocardial infarction, stroke, and heart failure [8]. Specifically, the risk is the most increased in women with recurrent preeclampsia or in those diagnosed with, preeclampsia associated with a preterm delivery, or intrauterine growth restriction of the fetus.

Fetal Outcomes

Placental perfusion is decreased in preeclampsia, frequently resulting in intrauterine growth restriction of the fetus and oligohydramnios. These findings may prompt preterm delivery of the fetus.

Fetal outcomes in pregnancies complicated by preeclampsia are largely influenced by gestational age at time of delivery. The frequency of neonatal complications such as necrotizing enterocolitis, respiratory distress syndrome, and intraventricular hemorrhage has been found to be similar in neonates of preeclamptic women matched with non-hypertensive controls [9].

Perinatal death is primarily related to premature delivery, placental abruption, and intrauterine asphyxia. According to Liu et al., the purported fetal death rate in a population-based cohort study is 10.8 per 1000 births in pregnancies complicated by eclampsia [10].

Management

Fetal monitoring: All women diagnosed with preeclampsia without severe features, gestational hypertension, and chronic hypertension are closely monitored from the time of their diagnosis until delivery. Fetal non-stress testing (fetal heart rate monitoring for a twenty minute period) and evaluation of the amniotic fluid index aid in assessing placental perfusion. Patients diagnosed with preeclampsia with severe features or

HELLP syndrome are admitted to the hospital for continuous fetal monitoring.

Laboratory monitoring: Patients diagnosed with preeclampsia without severe features should have weekly laboratory testing to assess for evidence of end organ damage. In cases of preeclampsia with severe features or HELLP syndrome, laboratory evaluation may be undertaken daily or multiple times a day (depending on the clinical situation) given the rapidity with which patients may decompensate.

Thrombocytopenia is the most common hematologic abnormality in patients with preeclampsia [1]. Although uric acid is not included in the diagnostic criteria for preeclampsia, it monitored carefully in patients with preeclampsia given its known association with worse fetal outcomes [11].

Timing of delivery: Given that the disease process of preeclampsia begins with placental issues, the cure is delivery of the fetus and placenta. For women diagnosed with preeclampsia without severe features, delivery is generally recommended at thirty-seven weeks gestation [12]. For women diagnosed with preeclampsia with severe features, delivery is recommended at thirty-four weeks gestation. However, prompt delivery is recommended in the case of maternal or fetal indication [1] (Table 3). If there are no contraindications, then induction of labor with the goal of vaginal delivery is attempted whenever possible.

Medical management: Antihypertensive therapy is reserved for preeclamptic patients with blood pressures greater than 160 mmHg systolic or 110 mmHg diastolic [1]. Commonly used antihypertensive medications for acute management of blood pressure include labetalol, hydralazine, and nifedipine (Table 4). Antihypertensive medications should be used to achieve a goal blood pressure of 140-160/90-100 mmHg, which decreases the risk of intracranial hemorrhage without significantly decreasing placental perfusion.

If maternal thrombocytopenia is present, there is data to suggest that corticosteroid administration (specifically, dexamethasone) may be beneficial in increasing platelet counts [13]. While corticosteroids may not impact significant clinical outcomes of HELLP, administration may be clinically worthwhile in specific situations.

Magnesium sulfate: The use of magnesium sulfate for seizure (eclampsia) prophylaxis is reserved for patients diagnosed with preeclampsia with severe features[1] and has been demonstrated to be superior to other anticonvulsant agents (such as phenytoin) [14]. The exact mechanism of action remains unknown; although it is thought that magnesium sulfate acts as a 1) vasodilator 2) protectant against cerebral edema and 3) central anticonvulsant [15].

Magnesium sulfate is given in an initial bolus of four to six grams followed by a maintenance intravenous dose of one to two grams per hour. The goal magnesium level in the blood is 4.8-8.4 mg/dL and should be monitored every six hours given the potential for significant toxicity and even maternal death (Table 5). Antidotes for magnesium toxicity include calcium gluconate (1 g IV) or 10% calcium chloride (500 mg IV). Magnesium sulfate administration is strictly contraindicated in patients with myasthenia gravis.

Prevention

Many interventions have been studied to address prevention of preeclampsia, given the potential for significant fetal and

Table 3: Maternal and Fetal Indications for Delivery before 34 Weeks Gestation in Preeclampsia with Severe Features.

Maternal Indications	Recurrent severe hypertension Progressive renal insufficiency HELLP syndrome Persistent thrombocytopenia Pulmonary edema Suspected placental abruption Eclampsia
Fetal Indications	Persistent oligohydramnios Severe intrauterine growth restriction Biophysical profile 4/10 Reversed end-diastolic flow on umbilical artery Doppler studies Recurrent variable or late decelerations during non-stress testing Gestational age >34 weeks

Table 4: Antihypertensive Medications Used in the Management of Preeclampsia.

Medication	Initial Dose	Max Dose	Pharmacokinetics	Route	Special Considerations
Labetalol	10 mg	220 mg (in 24 hours)	Onset: 2-5 minutes Peak: 5 minutes	IV	-May cause fetal bradycardia. -Avoid in patients with asthma, heart disease, heart failure. -Contraindicated in patients with methamphetamine use.
Hydralazine	5-10 mg	25 mg (in 24 hours)	Onset: 5-20 minutes Peak: 15-30 minutes	IV	-May cause maternal hypotension
Nifedipine	10 mg		Onset: 5-20 minutes Peak 30-60 minutes	PO	-May cause maternal tachycardia

Table 5: Magnesium Toxicity.	
Magnesium level (mg/dL)	**Effect**
9.6-12	Loss of deep tendon reflexes
12-18	Respiratory depression
24-30	Cardiac arrest

maternal morbidity/mortality. Unfortunately, no single intervention has been proven useful for primary prevention of preeclampsia. However, in a subset of women with prior pregnancy with preeclampsia and subsequent preterm delivery, use of aspirin has been identified as a beneficial therapeutic modality for risk reduction.

A 2007 Cochrane meta-analysis demonstrated a 17% risk reduction in preeclampsia with the use of anti platelet agents with a significant decrease in absolute risk in women at high risk for disease [16]. Thus, the American College of Obstetricians and Gynecologists (ACOG) Task Force on Hypertension in Pregnancy [1] recommends considering initiating the use of low-dose aspirin in the late first trimester for women with a history of preeclampsia with subsequent delivery at or before 34 weeks gestation.

Preconception counseling: For women with risk factors for preeclampsia (Table 2), preconception counseling presents an opportunity to identify potentially modifiable risk factors. Baseline laboratory studies should be obtained at the beginning of the pregnancy and the patient should be counseled about signs and symptoms of preeclampsia.

DISCUSSION & CONCLUSION

Preeclampsia remains one of the leading causes of maternal morbidity/mortality. It is important to recognize that preeclampsia represents one diagnosis on a continuum of pregnancy-related hypertensive disorders given the potential for their interplay. Prompt diagnosis and proper management can significantly impact outcomes for both mother and fetus.

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