

Virtual Mentor

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Clinical Pearl

Preeclampsia: A Perturbation of the Maternal-Fetal Balance?

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Introduction

Preeclampsia is a pregnancy-specific disorder that affects many organ systems and is recognized by new onset of hypertension and proteinuria after 20 weeks of gestation. Affecting 5-8 percent of all pregnancies, preeclampsia can cause substantial maternal, fetal, and neonatal morbidity and mortality. The term *eclampsia* is derived from Greek meaning “sudden flashing” or “lightning” and refers to the seizures that can accompany this syndrome. Although this disorder was described by the Egyptians and Indians more than 2,000 years BCE, the only known cure for preeclampsia remains delivery of the fetus and placenta.

In the developing world, preeclampsia and hypertensive disorders of pregnancy are among the leading causes of maternal mortality [1]. Although maternal death due to preeclampsia is less common in developed countries, maternal morbidity remains high worldwide and is a major contributor to intensive care unit admissions among pregnant women. The fetus is at increased risk for growth restriction and death. Iatrogenic preterm delivery and the associated complications of prematurity may also lead to neonatal death or serious neonatal morbidity [2].

Diagnosis

The nomenclature for preeclampsia has changed over the years, with terms such as “toxemia” and “pregnancy-induced hypertension” now considered outdated. The Working Group Report on High Blood Pressure in Pregnancy [3] defines mild preeclampsia as:

- new onset of sustained elevated blood pressure (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic), and
- proteinuria (at least 1+ on a dipstick or ≥ 300 mg in a 24 hour urine collection) first occurring after 20 weeks of gestation.

Preeclampsia is considered severe when any of the following is also present:

- blood pressure greater than or equal to 160 mmHg systolic or 110 mmHg diastolic,
- urine protein excretion of at least 5 grams in a 24 hour collection,
- neurologic disturbances (visual changes, headache, seizures, or coma),
- pulmonary edema,

- hepatic dysfunction (elevated liver enzymes or epigastric pain),
- renal compromise (oliguria or elevated serum creatinine concentrations),
- thrombocytopenia,
- placental abruption, fetal growth restriction, or oligohydramnios.

The term eclampsia is used when seizures occur with this disorder.

HELLP syndrome, often considered a variant of preeclampsia, is defined by the presence of hemolysis, elevated liver enzymes, and low platelets. Elevated blood pressure alone after 20 weeks of gestation is referred to as gestational hypertension, and gestational hypertension that resolves postpartum is called transient hypertension. Hypertension that persists beyond the postpartum period is considered to be chronic hypertension. These diagnoses often can be made only in retrospect, unless hypertension precedes pregnancy or develops before 20 weeks of gestation. Preeclampsia can also develop in women with chronic hypertension. This superimposed preeclampsia is characterized by a sudden and sustained increase in blood pressures with or without substantial increase in proteinuria.

Risk Factors

Preeclampsia is more common in first pregnancies and new paternity and in women with personal or family histories of preeclampsia, multifetal gestation (twins and above), obesity, or certain medical conditions such as hypertension, diabetes, certain thrombophilias, renal disease, and lupus. Paradoxically, cigarette smoking reduces the risk of preeclampsia.

Pathophysiology

Preeclampsia is more than just hypertension. It is a syndrome involving multiple organ systems that is characterized by vasoconstriction, endothelial dysfunction, activation of the coagulation cascade, oxidative stress, metabolic changes, and an excessive inflammatory response. Although extensive research in this arena is ongoing, the precise pathophysiology of preeclampsia is not yet known. Conceptually, preeclampsia can be thought of as having two stages [4]. The first stage—abnormal vascular remodeling of the maternal uterine spiral arterioles by invasive placental trophoblasts and reduced placental perfusion—occurs early in pregnancy and is considered the cause. The second stage—which includes the maternal syndrome of vascular dysfunction and multi-organ system involvement—is considered to be a consequence of the first stage. Current research focuses on two key questions: (1) why do some, but not all women, with reduced placental perfusion develop preeclampsia? and (2) what links the two stages?

Regarding the first question, recent research has focused on the interaction of maternal natural killer cells in uterine decidua and trophoblastic HLA-C antigens (major histocompatibility complex class I molecule) [5] because immune-mediated interactions at the maternal-fetal interface are important for signal regulation between the mother and fetus. Certain combinations of receptors on uterine natural killer cells and trophoblast HLA-C polymorphisms can lead to the abnormal vascular

remodeling and inadequate placental perfusion that is characteristic of preeclampsia. Such maternal-fetal interactions may, in part, explain the increased risk of preeclampsia in first pregnancies or new paternity and in women who have received donor eggs to achieve pregnancy.

Regarding the second question, the precise link(s) between reduced placental perfusion (stage 1, i.e., the cause) and the maternal syndrome (stage 2, i.e., the consequence) is not well understood. Teleologically there is no apparent benefit in severe maternal—and possibly fetal—illness during pregnancy. One proposed evolutionary theory is that preeclampsia is a case of maternal-fetal competition for limited maternal resources [6]. Normally, the fetus influences the flow of nutrients and blood which sustains it while not adversely affecting its mother's health. But adaptive fetoplacental signals to increase oxygen and nutrient delivery to the fetus may not be tolerated by certain women, resulting in an inappropriate or exaggerated maternal response that leads to the serious systemic manifestations observed with preeclampsia.

Recent research has focused on placenta-derived angiogenic growth factors and their role in the pathogenesis of preeclampsia. Prior to and with clinically recognized preeclampsia, circulating concentrations of anti-angiogenic factors, such as soluble vascular endothelial growth factor receptor—also known as soluble fms-like tyrosine kinase receptor-1 (sFlt-1)—and soluble endoglin are increased, while concentrations of pro-angiogenic factors such as placental growth factor are decreased [7, 8]. In rats, adenovirus transfection with sFlt-1 results in systemic features similar to preeclampsia [9]. Thus, sFlt-1 can be considered a fetoplacental signal that can result in a harmful maternal response.

Clinical Management

The only known cure for preeclampsia is delivery of the fetus and placenta [10]. Vaginal delivery is usually appropriate unless other obstetric complications indicate the need for or advisability of cesarean section. If preeclampsia becomes clinically apparent at term (greater than or equal to 37 weeks), delivery at that time benefits both the mother and the neonate. Intravenous magnesium sulfate is used to prevent seizures. In general, this approach results in favorable maternal and neonatal outcomes.

With pregnancies that are preterm, especially those less than 34 weeks of gestation, delivery provides clear maternal benefit but may be disadvantageous to the neonate because of the complications associated with prematurity, such as respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and developmental delay. Delaying delivery in early-onset or severe preeclampsia may be acceptable in certain circumstances [11] to improve neonatal outcome, but must be carefully considered so that maternal risks are not excessive. The health of the mother must be constantly weighed against the potential benefits of delayed delivery for the baby. Close inpatient maternal and fetal surveillance in a

tertiary care facility with 24-hour obstetric, neonatology, and anesthesia services is a necessity.

Women who have had preeclampsia are at increased risk for cardiovascular disease later in life [12, 13]. Many predisposing factors are common to both conditions [14]. Thus, preeclampsia may have implications for a woman's health over the course of her lifetime, and close follow-up is recommended.

Conclusion

Preeclampsia is a heterogeneous pregnancy disorder. Its precise cause is unknown, and research efforts are ongoing. We know that the normal balance between the mother's interests and those of the fetus are perturbed in pregnancies complicated by preeclampsia. While this perturbation may be adaptive in certain situations, the resultant imbalance can lead to serious complications for the mother and the baby. Striking an appropriate balance between maternal and fetal well-being can also be challenging in the clinical management of preeclampsia. The ultimate goal with preeclampsia and other pregnancy complications is a favorable outcome for both patients—the mother and the baby.

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