EDUCATIONAL COMMENTARY: ECLAMPSIA, PREECLAMPSIA, AND OTHER HYPERTENSIVE DISORDERS OF PREGNANCY

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Learning Objectives

On completion of this exercise, the participant should be able to

• differentiate preeclampsia from eclampsia, chronic hypertension, and gestational hypertension by symptoms, pathogenesis, and prognosis;
• characterize the etiologies of preeclampsia and eclampsia;
• outline the clinical laboratory professional's role in providing the critical laboratory testing for the diagnosis of preeclampsia and eclampsia; and
• discuss the cardiac and stroke risks and HELLP syndrome associated with preeclampsia and eclampsia.

Introduction

Pregnancy is one of the most common human experiences, and millions of births happen every year without complications to the mother or child. Although the connection between certain symptoms and poor pregnancy outcomes was described as early as Hippocrates,¹ it was not until 1619 that Varandaeus first used the term *eclampsia*, from the Greek word meaning “shine out,” to describe the flashing lights or spots before the eyes of pregnant women.² Early theories of the origin of this condition included an imbalance of body humors and a wandering uterus.³ Thousands of years of observational, anatomic, and physiologic investigations have only minimally advanced the understanding of the etiology of this pregnancy complication and the ability to predict its occurrence or outcome. Singh considered these conditions the “most significant and intriguing unsolved problems in obstetrics.”⁴ *Preeclampsia* first found its way into obstetric textbooks in 1903 and was included in the category of Toxemias of Pregnancy in 1966. By 1976, the obstetric community recommended that the category be replaced with Hypertensive Disorders of Pregnancy; finally, in 1988, preeclampsia was classified as a Pregnancy-Induced Hypertension.³ In addition to preeclampsia, other conditions classified as hypertensive disorders of pregnancy include eclampsia, gestational hypertension, chronic hypertension, and the combination of preeclampsia with chronic hypertension. Laboratory testing provides significant assistance in the differential diagnosis of these conditions.

Chronic Hypertension and Gestational Hypertension

Chronic hypertension is high blood pressure (defined as diastolic pressure 90 mm Hg or greater or systolic pressure 140 mm Hg or greater) that exists before pregnancy, or that develops before 20 weeks' gestation and persists after delivery. In contrast to preeclampsia/eclampsia, chronic hypertension is not
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associated with proteinuria. Treatment of this hypertension during pregnancy will not benefit the fetus (and may be teratogenic, if treatments such as ACE inhibitors are used), nor will it prevent the onset of preeclampsia.\textsuperscript{4,5} There is, however, a 30\% probability that a woman with hypertension at the beginning of her pregnancy will develop “severe” category preeclampsia.\textsuperscript{4} The proteinuria of preeclampsia will signal that this switchover has occurred.

Gestational hypertension, the most common hypertensive disorder of pregnancy, develops for the first time at 20 weeks’ gestation or later, similar to preeclampsia, but without the characteristic proteinuria of that condition. Saudan, et al. found that gestational hypertension has a decreasing likelihood of developing into preeclampsia as the pregnancy progresses, with the greatest risk if the hypertension is diagnosed before 30 weeks’ gestation.\textsuperscript{6}

**Pathogenesis of Preeclampsia**

Magee, et al. summarized preeclampsia as a “mismatch between utero-placental supply and fetal demands, leading to systemic inflammatory maternal and fetal manifestations.” Because placental delivery is the sole cure for the condition, research has focused on the placenta, specifically on the increased angiogenesis associated with its development, as the source of the pathogenesis of this disease.

In normal pregnancies, there is a remodeling of the uterine spiral arteries by an invasion of the embryonic cytotrophoblastic cells (Figure, left).\textsuperscript{8} These cells transform the arteries from thick-walled, muscular, and lined with an epithelium phenotype to wider, less rigid, and having a lining more like endothelium.\textsuperscript{9} This change allows for an overall normal hypervolemia, sufficient blood flow for the fetus, and lower-resistance blood vessels.\textsuperscript{10} In preeclampsia, this differentiation of the cytotrophoblast cells does not occur (Figure, right),\textsuperscript{8} leading to a cascade of events associated with narrower/higher-resistance blood vessels: decreased placental blood flow, hypoxia (which itself leads to endothelial damage in multiple organs, including the kidneys and liver\textsuperscript{11} and reduced fetal growth), and symptoms of

\begin{figure}[h]
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\includegraphics[width=\textwidth]{failure_of_physiological_transformation_of_the_spiral_arteries.png}
\caption{Failure of physiological transformation of the spiral arteries is implicated in preeclampsia.\textsuperscript{8} Copyright 2014. Reprinted with permission from the Nature Publishing Group.}
\end{figure}
proteinuris beginning after 20 weeks’ gestation. The vascular damage also seems to alter the balance of production of vasodilators (nitric oxide, prostacyclin) compared with vasoconstrictors (endothelin, thromboxane A), with the net result of overall increased blood pressure.9

A 2015 study by Rabaglino, et al. used a bioinformatics approach to investigate which differentially expressed genes (DEGs) in chorionic villus samples could distinguish normal trophoblast invasion from the abnormal placental vascular development of preeclampsia. They found that three genes associated with the early maturation of the placenta (predecidualization) as well as the number and function of decidual natural killer cells, detected before embryonic trophoblast invasion, were downregulated in women who later developed preeclampsia. Further analysis uncovered downregulation of 16 of 396 DEGs, which are upregulated in normal placental development.12

**Preeclampsia**

Kuklina, et al., using data from the 1998-2006 Nationwide Inpatient Sample, found mild or severe preeclampsia in a total of 1.2 million deliveries out of 36 million during that time period.13 Incidence of preeclampsia varies in the literature from 1% to 8%.4,7,14 At greatest risk are mothers who are primigravida, those with first-time pregnancies. It is unclear whether youth is a risk factor since this was not supported by a 2005 systematic review,15 although Singh mentioned it in 2013.4 The same systematic review found significant associations for preeclampsia with those who have a history of preeclampsia, antiphospholipid antibodies, diabetes mellitus, twin pregnancies, family history, or a delay of more than 10 years from a previous pregnancy.15 Women older than 35 who experience preeclampsia are usually those who are chronically hypertensive. Bodnar, et al. reported in 2005 that obesity “is the leading attributable risk for preeclampsia in the United States, present in 30% of cases.” Studies in the Netherlands in 2013 compared 197 women with a history of preeclampsia who either did or did not have metabolic syndrome between pregnancies.17 The investigators reported that women who had inter-pregnancy metabolic syndrome had nearly a four-fold increase in the presence of preeclampsia in a later pregnancy compared to those without.17

The major hallmarks of preeclampsia consist of high blood pressure (diastolic pressure 90 mm Hg or greater or systolic pressure 140 mm Hg or greater) and proteinuria greater than 0.3 g/day, developing after 20 weeks of pregnancy. The question of the relationship between level of proteinuria and maternal/fetal outcomes was addressed in a systematic review of the literature by Thangaratinam, et al. in 2009. They found that the severity of proteinuria is not a useful predictor of maternal or child outcomes. However, the authors advocated for further research into proteinuria in pregnancy, noting that of the 541 studies initially evaluated, only 16 met the criteria for inclusion in the review, and most of these had a small sample size.18
Severe preeclampsia is associated with diastolic pressure 110 mm Hg or greater, or systolic blood pressure 160 mm Hg or greater, twice over 6 hours while at bed rest; proteinuria greater than or equal to 5 g/day; and multiple significant complications. These complications can include headache, visual disturbances, upper abdominal pain, oliguria, creatinine that is 1 mg/dL over baseline, aspartate aminotransferase over 70 U/L, lactate dehydrogenase over 600 U/L, platelet counts less than 50-100 x 10^9/L, fetal growth impairment, stroke, and pulmonary edema. The liver/platelet/hemolysis components of this pattern are grouped into the HELLP syndrome, discussed below.

It is universally accepted that the only cure for preeclampsia is delivery of the baby and the placenta, with the placenta itself currently considered the major source of the abnormalities found in this condition. Scheduling the delivery involves a complex assessment of the stage of preeclampsia. Recommendations by Magee, et al. included immediate delivery for women with (1) severe preeclampsia regardless of gestational age, (2) preeclampsia at 37 weeks or later, and (3) HELLP syndrome at 35 weeks or later. If HELLP syndrome develops at 24 to 34 weeks’ gestation, delay in delivery is recommended, to allow corticosteroids to be administered to hasten fetal lung maturation.

Eclampsia

Eclampsia is distinguished from preeclampsia mainly by the development of seizures after the appearance of the other signs and symptoms of severe preeclampsia, when the seizures cannot be explained by other concurrent conditions. Women with severe preeclampsia may be given magnesium sulfate to prevent convulsions. Serum total or ionized magnesium can be monitored to warn of the possible effects of hypermagnesemia: loss of the patellar deep tendon reflex at 8 to 10 mEq/L, and respiratory paralysis seen at concentrations of magnesium greater than 13 mEq/L. The etiology of the cerebral symptoms and the mechanism for effective MgSO₄ treatment are not clear. They may be related to the disruption of the blood-brain barrier leading to cerebral edema, and MgSO₄ preventing that disruption.

Cardiovascular Risks and HELLP syndrome

Systolic blood pressure of 160 mm Hg or greater is associated with increased risk for stroke. Because it is strongly associated with both eclampsia and preeclampsia, high blood pressure alone places these patients at significant cardiovascular risk, with stroke and pulmonary edema resulting in a significant number of maternal deaths in these conditions.

HELLP syndrome is an acronym for “hemolysis, elevated liver enzymes, low platelet count,” and summarizes the findings initially described by Weinstein in 1982. Unfortunately, HELLP syndrome has a number of mimics, which can delay diagnosis: flu, gastritis, gallbladder conditions, and others.
Diagnosis is critical: the condition complicates 15% of pregnancies with preeclampsia, and the mortality rate of HELLP can be up to 25%. No single cause for the HELLP syndrome has been identified, but research centers on microvascular endothelial damage and platelet activation, leading to vasospasm and platelet aggregation. This can cause the low platelet count and the blood smear hemolysis evidence of spherocytes, schistocytes, and burr cells as the erythrocytes travel through narrow damaged blood vessels. In the liver, such damage can lead to sinusoidal blockage of blood flow, liver cell death, release of hepatic cell enzymes and, in the worst-case scenario, hemorrhage and even hepatic rupture. As in the case of eclampsia and preeclampsia, the only cure for HELLP is delivery of the child and placenta.

**Recommendations for Preventing Preeclampsia and Its Complications**

A major study reported in 2014 by the Canadian Hypertensive Disorders of Pregnancy Working Group summarized significant risk factors and recommendations for prevention of preeclampsia. Unfortunately, the authors could report no definitive clinical trials addressing prevention for women at high risk for the condition. Their recommendations were based mainly on studies conducted with women with low risk. For this population, low-dose aspirin and calcium supplementation were found to have high evidence of efficacy in prevention, whereas antihypertensive therapy (specifically to prevent preeclampsia) was not recommended. Among the treatment measures found to have insufficient evidence to recommend them for preventive purposes were exercise, garlic, iron plus folate, and multivitamins.

**New Testing on the Horizon**

Levine, et al. demonstrated in 2004 that the levels of two plasma proteins, fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PLGF), could be predictive of preeclampsia. Both of these proteins are associated with the tightly controlled balance between angiogenesis and antiangiogenesis involved in the normal development of the placental vasculature. A case-control study of 120 pairs of healthy primigravida women documented that sFlt-1 plasma levels significantly increased and PLGF levels significantly decreased at 13 to 16 weeks’ gestation in those women who later developed preeclampsia. This research has been translated into a diagnostic kit to measure PLGF within 15 minutes using an immunoassay platform, as a method of early diagnosis (Alere Triage® PLGF). The manufacturer’s website indicates that this product is not sold in the United States.

**Summary**

While preeclampsia remains a significant complication of pregnancies throughout the world, data suggest that better prenatal care leads to a decline in the rate of its occurrence. In addition, a 2013 revised guideline by the American College of Obstetricians and Gynecologists recommended against the sole use of proteinuria for preeclampsia diagnosis, mainly on the evidence that “many patients with preeclampsia
don't have enough proteinuria to meet the former criteria, so their diagnosis and treatment is delayed.\textsuperscript{28} These, coupled with new testing methods for predicting risk, suggest the 21\textsuperscript{st} century may see significant developments in the way preeclampsia is handled.

\textbf{References}


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