Preeclampsia; A Clinician’s Perspective

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When you’re asked to write an article for a publication known as The Laboratorian about a clinical disease which we see commonly however the pathophysiology is still quite an enigma presents quite the challenge. My charge here is to describe a pregnancy specific disease that can have tragic and dramatic consequences for both mother and child. I will focus on laboratory parameters that may shed light on an ongoing process that contributes to this devastating pregnancy specific condition. My only hope is that sooner or later you may define a pattern that will help us shed additional light on the etiology of this condition.

Preeclampsia is a disorder of pregnancy characterized by the development of hypertension, edema and proteinuria in the second half of pregnancy that was not present previously. It is commonly seen as pregestational proteinuric hypertension. Non-proteinuric hypertension usually makes a case for chronic essential hypertension complicating pregnancy. In years past the syndrome was considered when a patient presented with the triad of hypertension, edema, and proteinuria, however minor dependant edema is so common in pregnancy, it may have little impact. We will define the impact of edema later as severe is an issue as is in a patient with anasarca. Preeclampsia is characterized as either mild or severe. There is no “moderate” preeclampsia. Mild disease can be tolerated but severe needs treatment and the only effective treatment is delivery of the fetus. The pathophysiology is a multisystem, pregnancy related disease with varied risk factors, manifestations and presentation.

The etiology of this disorder has remained a mystery; however, those of us in obstetrics who see this complication often keep a very high index of suspicion when women present in pregnancy with elevated blood pressure. The hypertensive disorders of pregnancy occur in approximately 10% of pregnant women. Preeclampsia is one of the hypertensive disorders of pregnancy that also includes chronic essential hypertension and gestational hypertension. Both chronic essential hypertension and gestational hypertension probably have genetic/familial predilections that present in pregnancy due to the cardiovascular changes that occur. Preeclampsia can occur out of the blue with no predisposing risk factors and can also be seen as familial and/or “superimposed” on chronic essential hypertension which further varies among patients. It can present strictly as a maternal disorder with normal fetal development, or it can manifest as both a maternal and fetal disorder with in utero growth restriction (IUGR) or sudden fetal stress. The most common, tell-tale signs of PE are hypertension and proteinuria, however, additional maternal symptoms may occur including edema, endotheliosis, and renal or liver failure. In the most severe cases, this condition can progress to eclampsia or HELLP syndrome. PE can have an early onset (symptoms occur prior to 32 weeks gestation) or late onset (after 32 weeks). It is worthy to note that a higher morbidity rate is associated with early onset cases (1, 4).

The authors of this paper propose a mechanism akin to transplant rejection is associated with the process of preeclampsia. This hypothesis unites the observations that normal pregnancies are typified by T<sub>reg</sub>-mediated immune suppression while spontaneous abortion is T<sub>reg</sub>-mediated with the fact that a fetus is a semiallograft, having received half of its histocompatibility (MHC) antigens paternally. To solidify this notion, peripheral blood mononuclear samples from fourteen preeclamptic women were analyzed for the presence of cytotoxic T cells (CTL) specific to their partner’s MHC antigens. Fourteen gestational age and parity-matched samples were used as controls. The study revealed a greater number of paternal antigen-specific CTL was associated with the preeclamptic group and postulate this outcome is a result of the woman’s inability to properly suppress the immune response to these paternal factors and reach a state of immune tolerance. The authors often discuss the role of the maternal, the mixing of maternal and paternal polymorphic genes, as one possible explanation for this dichotomy.


During pregnancy proteinaceous vesicles, termed placental microparticles (MP), are shed from the outer layer of the placenta. These vesicles are shed in large quantities, which can be quantified using a new standard, the oneSwab<sup>®</sup>. During pregnancy these proteinaceous vesicles, termed placental microparticles (MP), are shed from the outer layer of the placenta. These vesicles are shed in large quantities, which can be quantified using a new standard, the oneSwab<sup>®</sup>. In the present study, the researchers aimed to determine whether the presence of MP was associated with clinical outcomes. The study was conducted at Mayo Clinic, and was based upon validated protocols from Schmitz et al. The study evaluated the presence of MP in 186 women with clinical outcomes. The researchers found that the presence of MP was associated with increased risk of preterm labor. This finding supports the hypothesis that the presence of MP is a potential biomarker for the prediction of preterm labor.


Amniotic fluid is considered to be sterile fluid and this belief has been born out for the majority of normal pregnancies. However, studies evaluating the possible breach of this microbiome by microbial organisms have demonstrated their presence in 18% of term pregnancies with intact membranes, 34% of women experiencing prelabor rupture of membranes, 13% of preterm births, 32% of PROM cases and 9% of women diagnosed with a short cervix. The authors of this paper argue that many cases get undiagnosed due to the fastidious nature of the infecting organisms and the reliance upon culturing techniques for their identification. Here the authors utilize the oneSwab<sup>®</sup> from a molecular standpoint, utilizing species discriminating PCR methodologies to determine the prevalence of microbial invasion of the amniotic cavity (MIC) and the causative agents. To this end, amniotic fluid from 62 preterm patients was examined by PCR for the presence of bacteria or yeast, unbalanced 25(OH)D levels, the long-lived TH2 immune responses while abnormal placentation and spontaneous abortion are TH1-mediated with the fact that a fetus is a semiallograft, having received half of its histocompatibility (MHC) antigens paternally. To solidify this notion, peripheral blood mononuclear samples from fourteen preeclamptic women were analyzed for the presence of cytotoxic T cells (CTL) specific to their partner’s MHC antigens. Fourteen gestational age and parity-matched samples were used as controls. The study revealed a greater number of paternal antigen-specific CTL was associated with the preeclamptic group and postulate this outcome is a result of the woman’s inability to properly suppress the immune response to these paternal factors and reach a state of immune tolerance. The authors often discuss the role of the maternal, the mixing of maternal and paternal polymorphic genes, as one possible explanation for this dichotomy.


This paper evaluated a possible correlation between decreased vitamin D levels and the phenomenon of preeclampsia. The study measured 25-hydroxyvitamin D levels in 250 women with early-onset severe preeclampsia, and 150 control women without pregnancy complications. The authors found that 50% of the EOSPE population was determined to be deficient in 25-hydroxyvitamin D, with 25(OH)D levels below 32 ng/mL. In addition, they found that African-American women had significantly lower levels of 25(OH)D compared to White women. The authors concluded that vitamin D deficiency is associated with increased risk of preeclampsia, and further research is needed to determine the exact mechanisms involved.

On November 2, 2010, the Centers for Medicare & Medicaid Services (“CMS”) finalized its proposed CY 2011 Medicare Physician Fee Schedule Rule which states that all test requisitions must be signed by the ordering physician in order to be reimbursed under the Clinical Laboratory Fee Schedule.

While CMS’s final rule states that this policy will go into effect on January 1, 2011, CMS has announced a delay to the implementation of this policy until April 1, 2011. As of April 1, 2011, all test requisitions paid under the Clinical Laboratory Fee Schedule must be signed by the ordering physician.

This new policy reverses CMS’s prior position that test requisitions do not need to be signed by the physician as long as the physician clearly documents in the patients’ medical records his or her intent that the test be performed. The reasoning behind CMS’s decision is that this new policy will require physician signatures on all laboratory test requisitions to eliminate all prior confusion surrounding the issue. Further, CMS stated that if the physician is already filling out the test requisition, there is no additional burden on the physician to sign the test requisition.

The laboratory community has been vocal in expressing its displeasure with CMS’s new policy and has requested that CMS push back the effective date of the new policy so that laboratories have sufficient time to educate their physician clients on the new policy and to ensure that the laboratory has sufficient administrative staff to handle the large volume of tests that will need to be put on hold due to a lack of physician signature on the test requisition.

Please note that the new signature requirements do not affect electronic orders or orders taken over the telephone. CLD appreciates your assistance in helping us comply with these new CMS requirements.

**LEGAL CORNER**

New CMS Physician Signature Requirements for Test Requisitions

By: Mark A. Lieberman, Esq., General Counsel and Theresa K. Segley, Esq., Compliance Officer

As of January 1, 2011, the following test replacement will take effect:

Discontinued

Test 176 Urinary Pathogens Antibiotic Resistance (E. coli, Klebsiella species, Proteus mirabilis)

Replacement

Test 146 Proteus mirabilis by Real-Time PCR

The following Test is being discontinued as of January 1, 2011:

Test 113 Herpes simplex virus (HSV) viral load by Real-Time PCR

**New Tests Available Beginning January 1, 2011:**

Available on OneSwab<sup>®</sup>

Test 172 Klebsiella species by Real-Time PCR (Reflex to Speciation by Pyrosequencing)

Test 175 Eggerthella species by Real-Time PCR

Available on NosoSwab<sup>®</sup>

Test 174 Pseudomonas aeruginosa by Real-Time PCR

Test 172 Klebsiella species by Real-Time PCR (Reflex to Speciation by Pyrosequencing)

Available on UroSwab<sup>®</sup> (Urines specimens only)

Test 146 Proteus mirabilis by Real-Time PCR

Available on UroSwab<sup>®</sup> (males only)

Test 174 Pseudomonas aeruginosa by Real-Time PCR

Available on UroSwab<sup>®</sup> (males & females)

Test 172 Klebsiella species by Real-Time PCR (Reflex to Speciation by Pyrosequencing)
Preeclampsia

To date, no preventative measures or effective treatments have been identified for preeclampsia (PE). Anti-hypersensitive drugs, corticosteroids, or magnesium sulfate may be administered to handle the symptoms of PE. Laresgoiti-Servitje et al., reported a shift toward Th1 responses and the increased production of IFN-γ associated with the origin of PE, Laresgoiti-Servitje et al., reported a shift toward Th1 responses and the increased production of IFN-γ associated with the origin of PE. Impaired trophoblast invasion may lead to deficient implantation, alterations in placental development, and inadequate blood supply and transport of nutrients (5).

In a review focused on examining the immunological factors associated with the origin of PE, Laresgoiti-Servitje et al., reported a shift toward Th1 responses and the increased production of IFN-γ associated with the origin of PE, Laresgoiti-Servitje et al., reported a shift toward Th1 responses and the increased production of IFN-γ associated with the origin of PE. Impaired trophoblast invasion may lead to deficient implantation, alterations in placental development, and inadequate blood supply and transport of nutrients (5).

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A: When attaching a print out of patient demographics to an MDL test requisition form, you must, at a minimum, write the patient name on the requisition. This does not, however, provide a cure; rather, the treatments are intended to adapt the patients to allow for the delivery of a more mature fetus. The only true resolution of PE is achieved through delivery of the fetus and removal of the placenta via induced labor or cesarean section (3).
Proteinuria, and vasoconstriction which is often reflected in the pregnant body disease with clinical findings of proteinuria and preeclampsia to be a multi-system total disease with clinical presentations with severe preeclampsia. Differentials also include thrombotic thrombocytopenic purpura (TTP) and erythromelalgia, which is defined as blood pressures over 160/110, with proteinuria, there are maternal renal disease. Early and high index of suspicion can go a long way to prevent the subcapsular hematoma rupture and exanguination all could have contributed to this patient's multisystem aspect of this disease.

Summary case study

Let's review some of the specific issues that occur in a woman with severe hypertension and proteinuria. Any patient with a normal pregnant woman presents with a blood pressure of 160/110, 4+ proteinuria, headache, scotoma, anuria, and is somnolent. The primary task here is to identify the cause of the hypertension, depending on the stage of gestation, secondarily monitor the fetal well-being. Aggressive control of blood pressure, seizure prophylaxis and placental and fetal surveillance are important. Proteinuria, up to 4+ of proteinuria, which is defined as blood pressures over 160/110, with proteinuria, there are maternal renal disease. Early and high index of suspicion can go a long way to prevent the subcapsular hematoma rupture and exanguination all could have contributed to this patient's multisystem aspect of this disease.

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complicates the well-being of the mother and fetus. Before embarking on a discussion of the hypertensive disorders of pregnancy, we must outline some of the basic concepts that accompany normal pregnancy at the earliest stages of gestation.

From just after conception, there are hormonal and cardiovascular changes that prepare the maternal system for the blood pressure, tachycardia, decrease in peripheral vascular resistance, and the beginnings of a dramatic increase in both cardiac output and intravascular volume. Of importance, however, is that the increase in gestational output times the total peripheral resistance, the blood pressure decrease in early pregnancy can only come about as a result of a dramatic decrease in total peripheral resistance.

It is due to many of these changes that we may see a decrease in an individual's blood pressure, which is part of the systemic gestational reaction. The fact that women may mask previously existing minor blood pressure elevations caused by chronic essential hypertension. As pregnancy advances, intravascular volume increases dramatically. We must be able to see cardiac decompression and that one may have to consider a peripartum cardiomyopathy, another potentially lethal pregnancy related disease.

The antiphospholipid antibody syndrome can produce a syndrome very similar to preeclampsia and also can consist of maternal thrombosis, fetal growth restriction and other multisystem complaints. The autoimmune component or inflammatory reaction at the endothelial level may all be common presentations with severe preeclampsia. Differentials also include thrombocytopenia and other forms of gestational hypertension, so this is a diagnosis of exclusion.

Some individuals have an invoked an inflammatory cause however the etiology is still very much unknown. That being said however there is no question that there is intense vasocostriction that often can be evaluated with Doppler ultrasound. Characteristic waveforms reflecting vasospasm in the maternal ureter may be an early screen, well before blood pressure increases, for the later development of this vasospastic condition we know as preeclampsia.

It was shown by Dr. Norman Gant years ago that a primigravida's blood pressure would increase with a very small dose of vasoconstrictor substance administered at mid pregnancy in women who were ultimately destined to become preeclamptic. Women who would become normotensive after pregnancy would need larger doses of vasoconstrictive type drugs to increase their blood pressure than their counterparts. This “preeclampsia predictor” defined individuals who would become preeclamptic up to eight weeks before the onset of symptoms suggesting there is a fundamental process ongoing well before the onset of hypertension. This study supported the idea that there was a vascular sensitivity in women destined to become preeclamptic not seen in women who would not become preeclamptic. This vascular sensitivity in normotensive individuals that was blunted in those becoming preeclamptic. This effect could be mediated as part of an adjustment of the rennin-angiotensin system by this sensitivity to angiotensin.

Women who are destined to become preeclamptic are known to have changes ongoing well before they have elevation of their clinically obtained blood pressure.

Even though the vast majority of women who developed preeclampsia early in their pregnancy have a “physiologic amenorrhea” due to increases in serum greater than red cell mass early in pregnancy. Elevations in hemoglobin and hematocrit usually as a result of vasoconstriction and can predate hypertension. Other lab findings including liver enzyme elevations, uric acid elevation, increases in BUN and creatinine often are subtle indices for preeclampsia.

In addition to proteinuria, the patient’s urine may show signs of red cell casts and her peripheral smear may show abnormal red cell morphology adding to the intrusion of an inflammatory or infective etiology.

There are numerous clinical factors that increase the risk for preeclampsia. They can include maternal age, primigravid status, multiple pregnancies (twins or higher order multiples), obesity, pre-existing hypertension, pregnancy induced hypertension, and collagen vascular diseases.

Physical findings and symptoms can also be associated with many of these risk factors. The onset of headache, scotomata, right upper quadrant abdominal tenderness, subconjunctival hemorrhage, and that one may have to consider a peri-partum cardiomyopathy, another potentially lethal pregnancy related disease.

Preeclampsia, one of the hallmarks of preeclampsia, is defined on a blood pressure of 140/90 in a pregnant woman that has had no prior history of hypertension. Preeclampsia occurs, the patient usually develops proteinuria, sometimes as much as nephrotic range proteinuria, with a higher hemoglobin and hematocrit. The usual pregnant patient has BUN and creatinine levels in the normal range, BUN and creatinine should be 50% of the nonpregnant norm. If the pregnant patient has BUN and creatinine levels in the normal range, BUN and creatinine should be 50% of the nonpregnant norm. If the pregnant patient has elevation of their clinically obtained blood pressure.

Doppler studies and sensitivity to vasopressors both suggest an early preclinical process ongoing that becomes a dramatic multisystem disease later. Conditions like molar pregnancy may, in some way, stimulate an clinical manifestation.

Blood pressure in a pregnant woman is monitored regularly throughout her pregnancy. Hypertension, defined as 140/90, with proteinuria, there are maternal renal disease, and collagen vascular diseases.

Other laboratory signs including liver enzyme elevations, uric acid elevation, increases in BUN and creatinine often are subtle indices for preeclampsia. This decrease in blood pressure that occurs early in pregnancy will often mask mild chronic essential hypertension that may have predated the pregnancy. As obstetricians generally deal with young women who may have never had their blood pressures monitored, this could be missed. Therefore, if a patient presents in the first trimester with hypertension, the blood pressure may have been taken many it may be significantly lower than it was prepregnancy. If their pressures are above the range of 120/80 in the first trimester. It has been shown that mean arterial pressure changes in pregnancy may go a long way to implicate the cause of the disease. Pressure changes in pregnancy may go a long way to implicate the cause of the disease. The blood pressure in a pregnant woman is monitored regularly throughout her pregnancy. Hypertension, defined as 140/90, with proteinuria, there are maternal renal disease, and collagen vascular diseases.

Seizures defines the progression from preeclampsia to eclampsia. Seizures are typically associated with a vascular sensitivity in women destined to become preeclamptic. Women of advanced maternal age who may also have previous hypertension, defined as 140/90, with proteinuria, there are maternal renal disease, and collagen vascular diseases.

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How do we prevent this type of tragic outcome?

Routine prenatal care along with risk factor identification could identify individuals as being at risk. These risk factors can include heredity, previous history and maternal medical diseases including pre-existing hypertension, collagen vascular disease, inflammatory diseases and renal disease. Early and high index of suspicion can go a long way to prevent this. The mother and infant require monitoring throughout the pregnancy.

As the disease progresses, it may be seen that the fetus has undergone uteroplacental insufficiency and growth restriction. In addition to the numerous maternal systemic abnormalities, this fetus had undergone uteroplacental insufficiency and growth restriction for some time. We may be a fictional case but one that every obstetrician has seen except for the rupture of the subcapsular hepatic hemorrhage. We can see from this scenario that the disease known as severe preeclampsia affects the mother and fetus. The relationship between the disease and the fetus is multifaceted. Hemodynamic changes include intravascular coagulation. The lungs and liver all showed evidence of petechial hemorrhage and congestion. A subcapsular hematoma of the liver had ruptured and there was free blood in the peritoneum. How do we prevent this type of tragic outcome?

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Preeclampsia

To date, no preventative measures or effective treatments have been identified for preeclampsia (PE). Anti-hypersensitive drugs, corticosteroids, or magnesium sulfate may be administered to handle the symptoms of PE. Lasero-Servitje et al., reported a shift toward Th1 responses and the increased production of IFN-γ in preeclamptic pregnancies. The source of IFN-γ remains elusive, however, its role in inhibiting trophoblast invasion is well established. The authors propose the observed shift towards a Th1 phenotype may also be the result of elevated IFN-γ. Further studies are necessary to identify the cells or antigens regulating the immune responses in PE as well as the precise mechanisms involved (5).

Recently, a group of researchers from New York identified a novel mouse model of immunologically-mediated pre-eclampsia. Ahmed and colleagues examined the CBA/J x DBA/2 mouse model to examine the effects of pravastatin in preventing the onset of PE. Pravastatin is an anti-cholesterol drug used in reducing the rate of incidence, continued research examining factors involved in the etiology and pathology of PE, as well as potential therapeutics will be of great value to the fields of gynecology and obstetrics.

REFERENCES:


Quality Assurance

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A: When attaching a print out of patient demographics to an MDL test requisition form, you must, at a minimum, write the patient name on the test requisition form. This enables our laboratory to confirm that the tests marked on the test requisition form are being ordered for that patient’s specimen. Demographics print out are an acceptable way to supply the additional information required.

The authors of this paper propose a mechanism akin to transplant rejection is associated with the process of pre-eclampsia. This hypothesis unifies the observations that normal pregnancies are tolerant to their partner’s MHC antigens, whereas pre-eclampsia is not. It suggests that the maternal immune system is not adequately tolerized to these paternal factors and reaches a state of immune tolerance. This tolerance is mediated by the presence of cytotoxic T cells (CTL) specific to the partner’s MHC antigens.


During pregnancy proteinaceous vesicles, termed placental microparticles (MP), are shed from the outer layer of the placenta and enter the maternal blood stream directly. Studies have indicated that these vesicles are associated with the occurrence of preterm labor. While there have been several reports linking the presence of MP to increased maternal blood pressure, a hallmark of pre-eclampsia, very few studies evaluated the composition of these particles in an attempt to explain their correlation. A few independent studies have evaluated the vesicle protein composition, including the tyrosine kinase sfl-1, which binds vascular endothelial and placental growth factors, as well as soluble endoglin, which binds transforming growth factor beta (TGF-β). However, the vesicle protein composition has not been extensively studied.

The laboratory community has been vocal in expressing its displeasure with CMS’s new policy and has requested that CMS push back the effective date of the new policy so that laboratories have sufficient time to educate their physician clients on the new policy and to ensure that the laboratory has sufficient time to educate their clients on the new policy. Further, CMS stated that if the physician is already filling out the test requisition, there is no additional burden on the physician to sign the test requisition.

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Preeclampsia: A Clinician’s Perspective

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When you’re asked to write an article for a publication known as The Laboratorian about a clinical disease which we see commonly however the pathophysiology is still quite an enigma presents quite the challenge. My charge here is to describe a pregnancy specific disease that can have tragic and dramatic consequences for both mother and child. I will focus on laboratory parameters that may shed light on an ongoing process that contributes to this devastating pregnancy specific condition. My only hope is that sooner than later you may define a pattern that will help us shed additional light on the etiology of this condition

Preeclampsia is a disorder of pregnancy characterized by the development of hypertension, edema and proteinuria in the second half of pregnancy that was not present previously. It is commonly seen as precipitated by familial hypertension. Non-proteinuric hypertension usually makes a case for chronic essential hypertension complicating pregnancy. In years past, the syndrome was considered when a patient presented with the triad of hypertension, edema, and proteinuria however minor dependant edema is so common in pregnancy, it may have little impact. We will define the impact of edema later when severity is an issue in a patient with anasarca. Preeclampsia is characterized as either mild or severe. There is no “moderate” preeclampsia. Mild disease can be tolerated but severe needs treatment and the only effective treatment is delivery of the fetus. The pathophysiology is a multisystem, pregnancy related disease with varied risk factors, manifestations and presentations.

The etiology of this disorder has remained a mystery; however, those of us in obstetrics who see this complication often keep a very high index of suspicion when women present in pregnancy with elevated blood pressure. The hypertensive disorders of pregnancy occur in approximately 10% of pregnant women. Preeclampsia is one of the hypertensive disorders of pregnancy that also includes chronic essential hypertension and gestational hypertension. Both chronic essential hypertension and gestational hypertension probably have genetic/familial predilections that present in pregnancy due to the cardiovascular changes that occur. Preeclampsia can occur out of the blue with no predisposing risk factors and can also be seen as familial and/or “superimposed” on chronic essential hypertension which further complicates the picture.

Preeclampsia

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Affecting 7% to 10% of pregnancies in the United States, Preeclampsia (PE) is the most common complication of pregnancy and remains a leading cause of maternal and fetal morbidity and mortality (1). More than 200,000 American women develop this disorder each year, the rate of incidence being equivalent to that of breast cancer. PE is characterized by hypertension (systolic and diastolic blood pressure of ≥ 140 and 90 mm Hg respectively) and proteinuria (protein excretion of ≥ 300mg in a 24 hour urine sample) which develops after 20 weeks gestation (1). Some women may develop high blood pressure without proteinuria which is referred to as pregnancy-induced hypertension. Although this too is a serious condition, it is not considered PE. Diagnosis of PE requires both elevated blood pressure (two separate BP readings must be taken at least six hours apart) and the detection of protein in the urine.

The clinical manifestation and progression of PE varies among patients. It can present strictly as a maternal disorder with normal fetal development, or manifest as both a maternal and fetal disorder with in utero growth restriction (IUGR) or sudden fetal stress. The most common, tell-tale signs of PE are hypertension and proteinuria, however, additional maternal symptoms may occur including edema, endotheliosis, and renal or liver failure. In the most severe cases, this condition can progress to eclampsia or HELLP syndrome (3). PE can have an early onset (symptoms occur prior to 32 weeks gestation) or late onset (after 32 weeks). It is worthy to note that a higher morbidity rate is associated with early onset cases (1, 4).