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Preeclampsia: Effect on the Fetus and Newborn

Ligia Maria Suppo de Souza Rugolo, MD,* Maria Regina Bentlin, MD,* Cleide Enoir Petean Trindade, MD*

Abstract
Preeclampsia (PE) is the most common medical complication in pregnancy and a major cause of maternal and fetal morbidity and mortality. This disease is a great challenge for obstetricians because there are no effective interventions to treat or prevent it, and antenatal care involves a difficult balance between the risks for women to continue pregnancy and the risks for the baby’s early birth. Fetal complications in PE are directly related to gestational age and the severity of maternal disease and include increased rates of preterm delivery, intrauterine growth restriction, placental abruption, and perinatal death. The major complications for the newborn are related to prematurity, although the data on the morbidity and outcome for preterm infants of women who have PE are conflicting, and few studies address this issue. The pathogenesis of PE involves abnormal placentation associated with immune and vascular events that result in endothelial dysfunction and clinical manifestations of PE. This disease has been associated with imbalance in angiogenic factors and oxidative stress. Nevertheless, only a limited number of studies have been carried out on fetuses and newborns that suggest that infants born from women who have PE are exposed to increased oxidative stress. Because oxidative stress and free radicals may play roles in several neonatal diseases, a direct effect of maternal disease on neonatal outcome is expected, and further research on such neonates, in the short- and long-term, is urgently needed.

Objectives After completing this article, readers should be able to:
1. Recognize the importance of PE.
2. Understand the pathophysiology of the disease and its related fetal effects.
3. Describe the most common fetal complications in PE.
4. Characterize the newborn whose mother has PE.

Incidence, Definition, and Risk Factors
Hypertensive disorders are the most common medical complications in pregnancy and major causes of maternal, fetal, and neonatal morbidity and mortality. Rather than clarify all the complex pathophysiology of PE, this article discusses some aspects that can help neonatologists understand the effects of the disease on the fetus and the newborn.

PE is a great challenge to obstetricians because its cause is unknown, its pathophysiology is complex and incompletely understood, its diagnosis may be difficult to determine, there are no effective treatments, and antenatal care involves a difficult balance between the risks for women to continue pregnancy and those for the baby’s early birth.

The disease can lead to many acute maternal complications, such as progression to eclampsia, acute renal or hepatic failure, pulmonary edema, and the HELLP syndrome (hemolysis, elevated levels of liver enzymes, and low platelet count). Furthermore, there is increased risk for long-term cardiovascular disease. (1)(2)(3)

Abbreviations
IUGR: intrauterine growth restriction
MDA: malondialdehyde
NHBPEP: National High Blood Pressure Education Program
NO: nitric oxide
PE: preeclampsia
PIGF: placental growth factor
sEng: soluble endoglin
sFlt1: tyrosine kinase
SGA: small for gestational age
TGF: transforming growth factor
VEGF: vascular endothelial growth factor

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The incidence of PE is about 5% to 10% of all pregnancies, with higher rates reported in first pregnancies, twin pregnancies, and in women who have had previous PE. Fifty percent of hypertensive disorders of pregnancy are defined as PE, the most important manifestation of the disease. (2)(4)(5) Among the several risk factors for PE are twin pregnancies, primiparity, previous PE, pregestational diabetes mellitus, chronic hypertension, and obesity. A family history of PE increases the women’s risk, suggesting a possible genetic predisposition. (1)(3)(6)

The most widely accepted definition and classification of hypertensive disorders of pregnancy was proposed by the National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Pregnancy, which used a blood pressure of 140/90 mm Hg or higher on two separate occasions at least 4 hours apart as the diagnostic criterion for hypertension. (7) The NHBPEP defined four hypertension categories in pregnancy: chronic hypertension, gestational hypertension, PE, and PE superimposed on chronic hypertension (Table 1) (Fig. 1).

PE is characterized as severe according to hypertension degree (arterial pressure ≥160/110 mm Hg on two occasions ≥6 hours apart); proteinuria (>5 g/24 hours or ≥3+ in two urine samples); or any of the following: cerebral/visual disturbances, abdominal pain, abnormal liver function, oliguria, pulmonary edema, thrombocytopenia, or fetal growth restriction. (1)

Pathophysiology
Although the cause of PE remains unknown, there are no doubts that the placenta is a triggering organ in development of the disease. Immune and vascular events have been implicated in the pathogenesis.

The Role of the Immune System
The innate/inflammatory response plays an important role during placentaion, with natural killer cells secreting cytokines, which promote the infiltration of spiral arteries by trophoblasts, thus causing a decidual inflammatory response. (1) (8) In this case, normal pregnancy has been viewed as a state of mild inflammation, and PE is associated with an intense systemic inflammatory response related to endothelial cell dysfunction and leukocyte activation. (9)

PE is considered a two-stage disease (Fig. 2) that begins with poor placentaion and reduced uteroplacental blood supply, resulting in placental hypoxia. This first stage, with silent placental events, is followed by the release of several mediators: growth factors and their soluble receptors, inflammatory cytokines, placental debris, and products of placental oxidative stress. Such mediators cause endothelial cell dysfunction and the systemic inflammatory syndrome, leading to the clinical manifestation of PE (second stage). (9)

The existence of two PE subsets of early and late disease that have different biochemical and clinical features was supported in a mouse model. The model showed marked pathologic changes in placentas, lower fetal survival, and more severe intrauterine growth restriction (IUGR) in early PE but no significant changes in placental and fetal growth in late PE, thus suggesting that early PE is a placental disease and late PE is a maternal systemic disease. (10) This finding could explain the poor outcome of fetuses and infants whose mothers develop early PE.

The Role of Oxidative Stress
Oxidative stress results from an imbalance between the increased generation of reactive oxygen species, including free radicals and the intermediates derived from the mitochondrial metabolism, and deficiency in antioxidant defense mechanisms. (11)

Placental oxidative stress is regarded as an intermediate event in the pathogenesis of PE, and although its cause

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnostic Criteria</th>
</tr>
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<tbody>
<tr>
<td>Chronic hypertension</td>
<td>Hypertension manifested before pregnancy, before 20 weeks of gestation, or persisting more than 12 weeks postpartum.</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>Hypertension manifested after 20 weeks of gestation.</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>Development of hypertension after 20 weeks of gestation, associated with proteinuria (≥0.3 g in a 24-hour urine specimen or ≥1+ on dipstick in two urine samples) in previously normotensive women.</td>
</tr>
<tr>
<td>Preeclampsia superimposed on chronic hypertension</td>
<td>Preeclampsia diagnosed in previously hypertensive women.</td>
</tr>
</tbody>
</table>

remains unclear, there is strong evidence that the triggering event is abnormal placentation with underperfusion, suggesting that increased oxidative stress could be generated in the placenta through the hypoxia-reperfusion mechanism. (12) Oxidative stress promotes lipid peroxidation in placental cell membranes and can lead to endothelial cell dysfunction through increased production of thromboxane A2, release of toxic products or activation of several intracellular signaling cascades, and secretion of soluble factors, which can subsequently activate the maternal inflammatory response. (13) Evidence that oxidative stress contributes to endothelial dysfunction, leading to PE, is supported by a number of reports showing increased concentrations of oxidative stress markers (usually malondialdehyde, a major breakdown product split off from lipid peroxides) in contrast with decreased antioxidant concentrations in maternal circulation and placentas of women who have PE. (14)(15)(16)

Nitric oxide (NO) dysfunction is another pathway involved in the pathogenesis of PE. NO is a major vasodilator, synthesized by endothelial cells from L-arginine. Endothelial dysfunction is characterized by decreased bioavailability of NO through reduced production or increased consumption by oxidative stress because NO is a highly reactive free radical. Endothelial cells can also produce methylated amino acids, such as asymmetric dimethylarginine, an endogenous competitive inhibitor of NO synthase, which has been found to be increased in women at risk for PE or IUGR. (13)(17) Decreased concentrations of NO in plasma and the placenta have been found in women who have PE, and although its role in the pathophysiology of PE has not been well defined, it is postulated that low NO concentrations might contribute through a lack of paracrine vasodilatory effect on the uteroplacental blood flow. (12)(18)

The pathogenic pathway of increased oxidative stress associated with deficient antioxidant defenses in PE is of great clinical relevance and has resulted in preventive supplementation strategies with vitamin antioxidants among pregnant women at high risk for PE. However, randomized, controlled supplementation trials with vitamins C and E did not demonstrate beneficial effects in the prevention of PE and low birthweight, even in popu-
lations that had low nutritional status from developing countries. (19) Possible explanations include inappropriate start time, vitamin dose, and spectrum to target oxidative stress. Further, oxidative stress may be a pathway in the pathogenesis and not the cause of PE.

Among antioxidants, glutathione peroxidase plays a critical role in the control of lipid peroxidation, and recent studies have reported significant reductions in maternal plasma and placental glutathione peroxidase activities in women who have PE. (16)(20)

In general, studies on oxidative stress-related complications in pregnancy have focused on maternal parameters. Although a limited number of studies have been carried out on fetal oxidative status and umbilical cord blood, the results have consistently shown an upregulation of oxidative stress markers and altered antioxidant status in fetal circulation. These data suggest that the fetus is affected by oxidative stress in PE and raise concern about fetal and neonatal outcomes. (14)(16)(21)

Ongoing research by our group at São Paulo State University aims to evaluate the role of oxidative stress on the neonatal outcomes of preterm infants born to women who have PE. Interesting preliminary results have been obtained. A prospective case-control study involved 30 preterm infants (<34 weeks of gestation) born to women who had PE and 30 gestational age-matched preterm babies born to normotensive mothers. The mean gestational age was 30 weeks. Glutathione, glutathione peroxidase, glutathione reductase, malondialdehyde (MDA), and NO were measured simultaneously in placental tissue, umbilical venous cord blood, and neonatal peripheral blood samples on the fourth day after birth. The same determinations were made in spot urine samples collected at postnatal days 1 and 4. The outcomes of interest included the incidences of respiratory distress syndrome, intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, and death during hospitalization. There were no differences in neonatal morbidity and mortality between the two groups. Oxidative stress changes were not found in the placenta, but they were detected in the umbilical venous blood and in urine on the first and fourth days after birth. Umbilical cord concentrations of glutathione and urinary concentrations of MDA correlated with neonatal outcomes. These results show that preterm infants of women who have PE are exposed to increased oxidative stress during the first days after birth, and despite no immediate clinical manifestation, the long-term outcomes are yet to be determined.

The Role of Angiogenic Factors

Placental angiogenesis is biphasic, with endothelial proliferation at mid-gestation and vascular remodeling in the second half of pregnancy. It is regulated by many growth factors, but vascular endothelial growth factor (VEGF) signaling represents a critical rate-limiting step. The placental growth factor (PIGF) is a member of the VEGF family, released by activated endothelial cells, which enhances the VEGF response. (22)

Expressed in endothelial cells, endoglin functions as a coreceptor for transforming growth factor (TGF)-β, which modulates its effects on angiogenesis. The soluble form of endoglin (sEng) has an antiangiogenic effect, inhibiting the TGF-β signaling pathway, and soluble forms, such as tyrosine kinase (sFlt1), are natural antagonists of VEGF-A and PIGF. Both of these antiangiogenic factors are increased in PE and correlate with complications, including placental abruption, IUGR, and early PE onset. sEng causes increased vascular permeability and hypertension, and its effects can be amplified by sFlt1. (22)(23) Experimental in vitro and human studies have suggested that an imbalance in angiogenic/antiangiogenic factors, represented by high concentrations of sFlt1 and sEng with low concentrations of PIGF and VEGF, causes endothelial cell dysfunction and is associated with PE development. (3) The precise mechanisms by which angiogenic factors participate in PE are not clear. Placental hypoxia has been considered to be the primary stimulus to sFlt1 release, although inflammatory mechanisms may also contribute. (23)

Increasing evidence suggests an important role for angiogenic factors on the pathophysiology of PE. A different profile in angiogenic/antiangiogenic balance may determine pregnancy outcome: PE or IUGR. In a case-control study, investigators demonstrated that changes in the proangiogenic factor (PIGF) and in antiangiogenic factors (sEng, sVEGFR-1) occur before PE development, with significant increases in angiogenic factors in the second trimester. Patients who had small-for-gestational-age (SGA) neonates showed no change in sVEGFR-1 but a higher concentration of sEng from the first trimester onward, suggesting a chronic antiangiogenic state that predisposes to SGA delivery. (22)

Currently, angiogenic factors are the most promising PE biomarkers and will continue being of utmost importance because they could allow early diagnosis, better management, and proper intervention. (3)
Genetics
Recently, epigenetic features, such as imprinting, and a growing number of genes have been implicated in the pathogenesis of PE, although the results are still not clear. Progress in this area should enhance the understanding of this disease by helping to identify new diagnostic biomarkers and propose preventive interventions. (1)(24)

New Information
New insights into the pathophysiology of PE have arisen from recent experimental studies using more reliable models and newer technologies. In a rat model of placental insufficiency using real-time polymerase chain reaction, a disturbed regulation in the expression of genes involved in blood pressure, angiogenesis, and immune cell regulation as well as an overexpression of genes related to the renin-angiotensin system were found, suggesting a role for this system in the pathogenesis of placental insufficiency. (24)

Obstetric Management
Despite some disagreement about obstetric monitoring and management of PE, there is no question that adequate prenatal care is the most important factor for early diagnosis and safe management of mothers and fetuses. Women in whom PE develops at or near term usually have mild disease and a favorable gestational outcome. In these cases, labor induction is effective and safe to prevent maternal complications. (25)(26)

The management of pregnancies that involve early severe PE is an issue of concern and debate between obstetricians and neonatologists because expectant management can positively affect perinatal outcome but may not be safe for the mother. A randomized, controlled trial addressing this issue (27) showed that expectant management of severe PE before 34 weeks of gestation improves neonatal outcome by delaying delivery by 1 to 2 weeks and reducing neonatal complications without increasing the risk for maternal complications. A systematic review assessing interventionist versus expectant care for PE before 34 weeks of pregnancy included only two randomized, controlled trials, and the data were insufficient for reliable conclusions about the best intervention. In the interventionist group, the risk for respiratory distress syndrome, necrotizing enterocolitis, and neonatal intensive care unit admission was higher, although babies were less likely to be SGA. (28)

As recently proposed by Colleta and Simpson, (26) PE management depends on gestational age, fetal status, and severity of maternal disease (Table 2).

Perinatal Outcome
The major issues are high perinatal mortality rates, IUGR, and increased neonatal morbidity due to preterm delivery. (4)(29) Uteroplacental insufficiency, placental abruption, and low gestational age are considered the primary factors associated with a poor perinatal outcome. (29) In addition, the influence of maternal disease severity, such as degree of hypertension, increased proteinuria, or the presence of HELLP syndrome, on perinatal outcome has been emphasized. (27)(30) It is noteworthy that the perinatal outcome should be modulated by the obstetric management of severe PE.

Severe proteinuria has been associated with the early onset of PE and early gestational age at delivery, with subsequent neonatal prematurity complications, although it does not seem to be an independent marker of adverse perinatal outcome. (27) The HELLP syndrome is associated with increased maternal mortality and morbidity; high perinatal mortality rates (200 to 400 in 1,000); and increased incidences of placental abruption, fetal distress, and IUGR. Prompt delivery is usually recommended. (30)

Mortality
Perinatal mortality rates range from 59 in 1,000 in developed countries to more than 300 in 1,000 in low-income countries, and they are influenced by viability thresholds. (2) Rates greater than 200 in 1,000 are usually reported in early severe PE at 24 to 34 weeks of gestation, and extremely high rates of more than 800 in 1,000 are seen with severe PE at 24 or fewer weeks of gestation (Fig. 3). Perinatal mortality is increased in infants affected by IUGR or asphyxia. (27)(31)

Current stillbirth rates in PE range between 9 and 51 in 1,000 births. Women with PE superimposed on chronic hypertension are 4.4 times more likely to have a stillbirth. (26)

IUGR
Fetal growth restriction is the issue of most concern. Although the relationship between IUGR and PE has been controversial, a high incidence of SGA infants in women who have PE has been reported, ranging from 15% to more than 50%. (4)(32) A retrospective cohort study showed that about 15% of pregnancies affected by IUGR later developed PE. (33) An analysis of a large database from the World Health Organization investigated whether PE, gestational hypertension, and IUGR
are related conditions. (5) PE and gestational hypertension groups had similar risk factors and neonatal outcomes. However, risk factors differed for PE and IUGR, and although both diseases increased fetal and neonatal mortality and prolonged neonatal intensive care unit stay, only PE increased the risk for preterm delivery. The authors concluded that PE and IUGR appear to be independent entities.

The relationship between IUGR and PE severity as well the possible confounding effect of chronic hypertension on the risks for IUGR in PE was investigated in a well-designed prospective case-control study. (34) The prevalence of chronic hypertension was 16% and 5% in the PE and control groups, respectively. Women who had PE had an increased risk for IUGR, especially those who did not have chronic hypertension. Among patients who had chronic hypertension, PE development did not affect the risk for IUGR, suggesting different pathways of fetal growth impairment. There was moderately increased risk for IUGR among severe cases compared with mild cases of PE. These findings emphasize that PE is independently associated with IUGR, but they could not confirm the value of IUGR in the diagnostic criteria of severe PE.

New Information

An interesting finding that contributed to the understanding of PE- and IUGR-related mechanisms was recently reported by Soto and associates. (35) The authors focused on complement system activation because it has been associated with vascular injury, growth restriction, and fetal death. Complement activation generates split products (C3a, C4a, C5a) that have proinflammatory properties, leading to increased vascular permeability, smooth muscle contraction, and chemotaxis of inflammatory cells. The aim of the study was to determine the profile of maternal complement split products in women who had SGA pregnancies, PE, and PE with SGA pregnancies. Higher C5a concentrations were found in PE (with or without SGA) compared with SGA pregnancies, suggesting that C5a participates in leukocyte activation and inflammation. This finding reinforces the role played by the innate immune system in the pathogenesis of PE, but complement activation was not observed in women who had SGA pregnancies. These results showed that PE and SGA pregnancies have different profiles: PE is a systemic maternal disease that can be associated with fetal growth restriction; SGA pregnancy is primarily a fetal disease.

Prematurity

Epidemiologic studies have reported alarmingly high rates of preterm births, predominantly due to increasing indications for preterm delivery, and PE is one of the most common of these indications. (1)(2)(4) Prematurity per se has a major impact on neonatal mortality and morbidity, but preterm newborns of women who have PE are of great concern because strong evidence shows that they are exposed to increased oxidative stress, which has been implicated in the pathogenesis of serious diseases in neonates. (11) Thus, an unfavorable outcome could be expected in infants of women who have PE. (2)(4)(32) However, reports of the early neonatal out-

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Table 2. Management of Preeclampsia

<table>
<thead>
<tr>
<th>Severity of Disease</th>
<th>Gestational Age</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Any</td>
<td>Control for severe disease and fetal growth Consider delivery at 37 weeks' gestation</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;24 weeks</td>
<td>Delivery</td>
</tr>
<tr>
<td></td>
<td>24 to 34 weeks</td>
<td>Administer corticosteroids for fetal lung maturation Administer antihypertensives, magnesium sulfate Consider delivery if there is maternal or fetal risk</td>
</tr>
<tr>
<td></td>
<td>&gt;34 weeks</td>
<td>Delivery</td>
</tr>
</tbody>
</table>

Figure 3. Perinatal mortality in preeclampsia according to gestational age. Data from Haddad and Sibai. (27)
come in infants of hypertensive mothers are conflicting (Table 3). In addition, PE may have long-term consequences for preterm and SGA infants. (2)(29)(46)

It is still unclear whether preterm infants born to women who have PE may have worse outcomes than those delivered preterm for other causes. It is also unclear whether the increased adverse perinatal outcome in these infants is due to shorter gestation or if there is a direct effect of maternal disease or treatment on the fetus and newborn. This is a very important line of investigation, considering the multiple mediators involved in the pathogenesis of PE. Further research is needed for better characterization of infants of women who have PE and to aid in predicting risks in their neonatal and later outcome.

Conclusion
PE remains a major obstetric problem because it is typically an unpredictable maternal disease with variable degrees of fetal involvement. Progress has been made in understanding the complex immunologic, vascular, and genetic factors involved in the pathophysiology of the disease, but to date, such progress has not been translated into clinical practice. No significant improvement has been observed in pregnancy and perinatal outcomes. PE remains an important cause of maternal and fetal morbidity and mortality. Early severe PE and IUGR deserve special attention from obstetricians and neonatologists.

Table 3. Neonatal Complications in Pregnancies Involving Preeclampsia

<table>
<thead>
<tr>
<th>Problem</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress syndrome</td>
<td>No difference in incidence; lung maturity is not accelerated in PE. (36)(37)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Associated with low birthweight and prematurity; early manifestation and transient course. (38)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>High incidence in the first 72 hours after birth and may be associated with increased risk of infection. (39)(40)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>Increased risk, primarily newborns who have intrauterine growth restriction. (41)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage/ periventricular leukomalacia (IVH/PVL)</td>
<td>Increased neonatal encephalopathy in term neonates. (42)</td>
</tr>
<tr>
<td></td>
<td>No difference or decreased incidence of IVH and PVL in preterm infants. (43)(44)</td>
</tr>
<tr>
<td></td>
<td>Neuroprotective effect of magnesium sulfate. (45)</td>
</tr>
<tr>
<td></td>
<td>No difference or decreased incidence of IVH and PVL in preterm infants. (43)(44)</td>
</tr>
<tr>
<td></td>
<td>Neuroprotective effect of magnesium sulfate. (45)</td>
</tr>
</tbody>
</table>

References
16. Boutet M, Roland L, Thomas N, Bilodeau JF. Specific systemic antioxidant response to preeclampsia in late pregnancy: the study of
NeoReviews Quiz

1. A previously healthy 21-year-old primigravid woman carrying a singleton fetus seeks consultation at an estimated gestational age of 24 weeks. Her blood pressure ranges from 142 to 148 mm Hg (systolic) and from 92 to 96 mm Hg (diastolic). She is complaining of abdominal pain and has proteinuria (urinary protein loss > 2.5 g/24 hours). Her liver function test results and blood counts are normal. Abdominal ultrasonography reveals a normal fetus with appropriate growth for gestational age. Of the following, the most accurate designation for the hypertensive disorder of pregnancy in this woman is:
   A. Chronic hypertension.
   B. Eclampsia.
   C. Gestational hypertension.
   D. HELLP syndrome.
   E. Preeclampsia.

2. Preeclampsia is classified as early or late disease, based on specific clinical, biochemical, and histopathological characteristics. Of the following, early preeclampsia is believed to be a:
   A. Fetal disease.
   B. Maternal autoimmune disease.
   C. Maternal free radical disease.
   D. Maternal inflammatory disease.
   E. Placental disease.

3. Several biomarkers have been studied in pregnant women to allow for early detection of preeclampsia and timely intervention. Of the following, the most promising biomarkers for preeclampsia are:
   A. Angiogenic factors.
   B. Complement split products.
   C. Free radicals.
   D. Inflammatory cytokines.
   E. Nitric oxide synthases.

4. The management of preeclampsia, including delivery of the infant, depends on gestational age, fetal status, and severity of maternal illness. Of the following, the optimal time for delivery in a pregnancy complicated by mild preeclampsia first observed at 28 weeks’ gestation is at a gestational age of:
   A. 28 weeks.
   B. 31 weeks.
   C. 34 weeks.
   D. 37 weeks.
   E. 40 weeks.

5. Preeclampsia has several adverse effects on the perinatal outcome. Of the following, the most common perinatal complication of preeclampsia is:
   A. Fetal growth restriction.
   B. Maternal cerebrovascular stroke.
   C. Neonatal periventricular leukomalacia.
   D. Neonatal respiratory distress.
   E. Placental abruption.
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