Preeclampsia and eclampsia: the conceptual evolution of a syndrome

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Preeclampsia, one of the most enigmatic complications of pregnancy, is considered a pregnancy-specific disorder caused by the placenta and cured only by delivery. This article traces the condition—once thought to be a disease of the central nervous system, recognized by the occurrence of seizures (ie, eclampsia)—from its origins to the present time when preeclampsia is conceptualized primarily as a vascular disorder. We review the epidemiologic data that led to the recommendation to use diastolic hypertension and proteinuria as diagnostic criteria, as their combined presence was associated with an increased risk of fetal death and the birth of small-for-gestational-age neonates. However, preeclampsia is a multisystemic disorder with protein manifestations, and the condition can be present even in the absence of hypertension and proteinuria. Toxins gaining access to the maternal circulation have been proposed to mediate the clinical manifestations—hence, the term “toxemia of pregnancy,” which was used for several decades. The search for putative toxins has challenged investigators for more than a century, and a growing body of evidence suggests that products of an ischemic or a stressed placenta are responsible for the vascular changes that characterize this syndrome. The discovery that the placenta can produce antiangiogenic factors, which regulate endothelial cell function and induce intravascular inflammation in the mother, has been a major step forward in the understanding of preeclampsia. We view the release of antiangiogenic factors by the placenta as an adaptive response to improve uterine perfusion by modulating endothelial function and maternal cardiovascular performance. However, this homeostatic response can become maladaptive and damage target organs during pregnancy or the postpartum period. Early-onset preeclampsia has many features in common with atherosclerosis, whereas late-onset preeclampsia seems to result from a mismatch of fetal demands and maternal supply, that is, a metabolic crisis. Preeclampsia, as it is understood today, is essentially a vascular dysfunction unmasked or caused by pregnancy. A subset of patients diagnosed with preeclampsia are at greater risk for the subsequent development of hypertension, ischemic heart disease, heart failure, vascular dementia, and end-stage renal disease. Given the toll on maternal and infant health as well as the long-term consequences of the syndrome, the understanding, prediction, prevention, and treatment of preeclampsia are healthcare priorities.

Key words: acute fatty liver, albuminuria, angiogenic factor, biomarker, blood pressure, cardiovascular disease, chronic hypertension, convulsion, eclampsia, edema, fetal death, genetic predisposition, gestational hypertension, great obstetrical syndromes, Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome, history, hypertension, hysterotonin, imitator, ischemia, placental growth factor (PIGF), postpartum preeclampsia, pregnancy-induced hypertension, proteinuria, severe preeclampsia, soluble fms-like tyrosine kinase-1 (sFlt-1), small for gestational age (SGA), stillbirth, toxemia, toxin, uteroplacental ischemia, vascular endothelial growth factor (VEGF)
Introduction
Preeclampsia is a syndrome considered unique to pregnant women; its causes, pathophysiology, prediction, management, and prevention present formidable challenges. This article reviews the conceptual evolution of this disorder.

An Enigmatic Pregnancy-Specific Disorder
Convulsions in pregnant women: epilepsy vs eclampsia
For centuries, ancient texts from Egypt, China, India, and Europe have recorded that pregnant women were at greater risk for seizures (Figure 1). Convulsions were reported to occur more frequently in primigravidae, both antepartum and postpartum, and to have a poor prognosis. A fundamental issue was whether seizures represented epilepsy or a unique, specific complication of pregnancy. The term “eclampsia” (derived from the Greek eklampsis, meaning “a shining forth”) was introduced by Johannes Varandaeus. François Boissier de Sauvages de Lacroix, a French physician and botanist interested in the taxonomy of diseases, is credited with distinguishing eclampsia from epilepsy. He proposed that eclampsia differed from epilepsy because the latter was chronic and recurrent throughout the life span while Eclampsia parturientium did not.

Convulsions and albuminuria
The association of convulsions, edema, and albuminuria was reported in 1843 by John C. W. Lever at Guy’s Hospital in London, England, and James Young Simpson at the University of Edinburgh, Scotland. Lever was interested in the similarities between patients with eclampsia and those with glomerulonephritis, who were cared for by Richard Bright at Guy’s Hospital (glomerulonephritis was known as “Bright’s disease” at the time). Lever tested the urine of 10 women diagnosed with puerperal convulsions and found albumin in most cases (9/10) (Figure 2). The exception was a patient who died from meningitis. Lever proposed that eclampsia differed from glomerulonephritis because albuminuria disappeared after delivery.

The triad: hypertension, albuminuria, and edema
Hypertension was recognized as a feature of eclampsia in 1885 by John William Ballantyne at the University of Edinburgh, who reported abnormalities in sphygmographic tracings (Figure 3) in three cases of pregnant women with “Bright’s disease.” Tracings were obtained during pregnancy, labor, and the postpartum period. Glomerulonephritis had been suspected in these cases given the combination of edema and albuminuria. Some have credited Louis Henri Vaquez and Pierre Nobécourt in 1897 with the discovery of eclamptic hypertension.

The origin of the term “preeclampsia”
The association of hypertension, proteinuria, and convulsions was subsequently confirmed by other investigators, and importantly, some noted that hypertension and proteinuria were present before seizures, hence the name “preeclampsia.” Leon Chesley credited the introduction of this term to John Clarence Webster in 1903 in the United States and to Bar in France (eclampsisme, meaning eclampsia without convulsions). The concept took hold and has since been a driving force in the organization of prenatal care, which is largely structured to detect preeclampsia by measuring blood

FIGURE 1
The Kahun Gynaecological Papyrus

A, The Kahun Gynaecological Papyrus was a medical text from the late Middle Kingdom (1850–1700 BC) addressing women’s health. The Papyrus was found near the modern-day Egyptian town of El Lahun in 1889 by Flinders Petrie. The Kahun Gynaecological Papyrus (UC 32057) is housed at University College London, London, United Kingdom. Pages 1, 2, and 3 of Plate VI are shown in the figure. Information was obtained from https://en.wikipedia.org/wiki/Kahun_Gynaecological_Papyrus.

B, The Kahun Gynaecological Papyrus was translated in 1893 by Frederick Griffiths and published as “The Petrie Papyri: hieratic papyri from Kahun and Gurob (principally of the Middle Kingdom).” The figure shows the translation of Prescription No. XXXIII from page 3 of the Plate VI (Medical Papyrus). It describes a cure to prevent a woman from biting her tongue the day of birth.

pressures, proteinuria, and by increasing the frequency of prenatal visits as term approaches.

“Toxemia of pregnancy”

Eclampsia and preeclampsia were originally attributed to “toxins” or “poisons” believed to enter the maternal circulation—hence, the term toxemia of pregnancy.1,11-13 Although there was debate14 over whether the source of the toxins was exogenous or endogenous. One exogenous source was thought to be bacteria, and Gerdes proposed that eclampsia was caused by products of a bacillus, which he named Bacillus eclampsiae.15,16 The endogenous sources (autotoxins) were proposed to be metabolic products of the fetus, mother, or placenta.17 The term “toxemias of pregnancy” included eclampsia, hyperemesis gravidarum, acute yellow atrophy of the liver, pruritus gravidarum, and ptyalism.18

The search for the toxins responsible for preeclampsia and eclampsia has lasted for more than a century. In 1914, James Young reported an association between placental infarctions and eclampsia and showed that placental extracts administered to guinea pigs induced seizures and other pathologic abnormalities.19 Subsequently, Hunter and Howard20,21 demonstrated the presence of a “pressor substance” in placental and decidual extracts as well as in the plasma of patients with preeclampsia: they named this substance hysterotonin. Later, Tatum and Mulé obtained whole blood from patients with severe preeclampsia and retransfused it into the same patients after delivery, resulting in a transient, but significant, increase in systolic and diastolic blood pressure.22 Similar observations were made by Pirani and MacGillivray,23 who collected plasma from pregnant women and then retransfused aliquots on postpartum day 6 and at six weeks after delivery (Figure 4). Plasma from patients with preeclampsia—but not normal pregnancy—elicited a hypertensive response on postpartum day 6. This finding led to the conclusion that a soluble factor present in the plasma of patients with preeclampsia could induce hypertension—supporting the concept of a circulating “toxin.” However, when a similar aliquot of plasma was retransfused six weeks after delivery, hypertension did not occur. This was interpreted as indicating that the increased vascular response of patients to the circulating pressor substances (toxins) had disappeared. This conclusion was strengthened by subsequent observations that women with preeclampsia and those destined to develop preeclampsia are more sensitive to the pressor effects of angiotensin II.24 The search for the “toxins” has continued to date, but the use of the term “toxemia” has progressively been abandoned. The anti-angiogenic factor (soluble fms-like tyrosine kinase-1 [sFlt-1]) has emerged as a major candidate for one of the “toxins” responsible for preeclampsia.

A Shift in Focus: From Maternal Signs to Fetal and Neonatal Adverse Outcomes

A major change in the conceptualization of preeclampsia and eclampsia occurred when investigators refocused the emphasis from maternal health outcomes (eg, seizures and death) to fetal and neonatal outcomes (eg, fetal death, fetal growth restriction, and small-for-gestational-age [SGA]). Two major studies conducted in the United States shaped the classification of hypertensive disorders and the importance of proteinuria.25,26 Page and Christianson25 reported the results of a prospective study of nearly 13,000 pregnancies between 1959 and 1967, which were part of the Child and Health Development studies conducted in the United States. Patients were classified according to the mean arterial blood pressure measured in the second and third trimesters and to the presence or absence of proteinuria. Preeclampsia was defined as an elevated blood pressure in the third trimester with six weeks after delivery.
proteinuria. If the patient presented with an elevated blood pressure in the second trimester, the disorder was considered to represent chronic hypertension.\textsuperscript{25} The major finding of the study indicated that the rate of fetal death was higher in patients diagnosed with preeclampsia or chronic hypertension, but not in those with gestational hypertension (Figure 5).\textsuperscript{25} Of interest, proteinuria (defined as 2+ or greater) was also a risk factor for fetal death, regardless of the presence of hypertension.

A major epidemiologic effort to examine the relationship among blood pressure, proteinuria, and adverse pregnancy outcome was undertaken as part of the Collaborative Perinatal Project, sponsored by the National Institutes of Health, which began in 1958 and prospectively enrolled 58,806 pregnancies at 12 university centers in the United States.\textsuperscript{26} The results of the systematic evaluation of blood pressure, proteinuria, and pregnancy outcome were published in the book “Pregnancy hypertension” by Friedman and Neff (Figure 6).\textsuperscript{26} One of the conclusions of this study was that edema, whether diagnosed by history or by physical

**FIGURE 3**
First demonstration of hypertension in eclampsia

IV.—SPHYGMOGRAPHIC TRACINGS IN Puerperal ECLAMPSIA.
By J. W. Ballantyne, M.B., C.M., Buchanan Scholar.

(Read before the Edinburgh Obstetrical Society, 14th January 1885.)

Mrs. R.—Bright’s disease in pregnancy. Pulse of high arterial tension. (2 ½ oz.)

Mrs. W.—Second day of Puerperum; change in characters; tension increased; marked tidal or predicrotic wavelet. (4 oz.)

The sphygmographic tracings record blood pressure from women with preeclampsia (A) during pregnancy and (B) in the postpartum period. Modified from Ballantyne.\textsuperscript{8}

**FIGURE 4**
Evidence supporting the existence of circulating “toxin(s)” in preeclampsia: autotransfusion of maternal blood induces hypertension

A Autotransfusion on postpartum day 6

B Autotransfusion 6 weeks after delivery

Changes in diastolic blood pressure in patients with preeclampsia and controls (A) on postpartum day 6 and (B) at 6 weeks postpartum after plasma autotransfusion. Modified from Pirani and MacGillivray.\textsuperscript{23}

examination, had minimal influence on outcome. This observation strengthened the case to remove edema from the triad of hypertension, proteinuria, and edema, which had formerly been used to diagnose preeclampsia. Moreover, the study was key in generating important data about the relationships among hypertension, proteinuria, and adverse pregnancy outcome.

Table 1 shows the rate ratios of fetal mortality by diastolic blood pressure according to gestational age. Before 36 weeks of gestation, fetal mortality was associated with values of \( \geq 85 \text{ mm Hg} \) (diastolic blood pressure). After 36 completed weeks of gestation, fetal mortality was associated with a diastolic blood pressure of \( \geq 95 \text{ mm Hg} \). Moreover, fetal mortality was associated with proteinuria exceeding \( 1+ \), and the greater the proteinuria, the higher the risk of fetal mortality (Table 2). Importantly, a synergistic effect was noted between diastolic blood pressure and proteinuria (Figure 7). For example, fetal mortality was increased 9-fold (Table 3, red circle) if diastolic blood pressure (95–104 mm Hg) and proteinuria 2+ were present. The data from the Collaborative Perinatal Project indicated that an elevation in systolic blood pressure was associated with virtually the same fetal outcome as an elevation in diastolic blood pressure. However, diastolic pressure was considered a better risk indicator than systolic pressure, given that low systolic pressure was not associated with a poor outcome but low diastolic pressure was.

The clinical implementation of these observations followed the recommendation of the World Health Organization and the American College of Obstetricians and Gynecologists (ACOG). The selection of 90 mm Hg as a cutoff value for diastolic blood pressure was made because it is a midpoint between 85 mm Hg and 95 mm Hg (85 mm Hg was associated with fetal mortality when combined with proteinuria, and 95 mm Hg was associated with fetal mortality regardless of proteinuria). Recent recommendations of the American College of Cardiology and the American Heart Association to lower the threshold for the diagnosis of hypertension in nonpregnant subjects to 130/80 mm Hg \(^{27}\) have now stimulated a dialogue about whether the threshold should also be applied to the diagnosis of preeclampsia. \(^{28,29}\) Early evidence suggests that perinatal outcomes in pregnant women with stage 1 hypertension before 20 weeks of gestation are worse than those with normal blood pressure (stage 1 hypertension is defined as BP range 130-139/80-89 mm Hg). \(^{30}\) However, more work is necessary to determine whether the diagnostic criteria should be modified.

**Preeclampsia: More than Pregnancy-Induced Hypertension**

The hallmark of the clinical diagnosis of preeclampsia has been hypertension. However, the involvement of other organs has been known for decades based on autopsy findings and clinical reports (Figure 8). The most frequent organs involved are the kidney (proteinuria), liver (elevation of transaminases, liver hematoma, and rupture), hematopoietic system (hemolysis, leukocytosis, and thrombocytopenia), brain (seizures, cortical blindness, intracranial hemorrhage, and infarction), and uteroplacental circulation (fetal growth restriction, abortion, and fetal death). Other organs and systems that may be involved include the lung (ventilation-perfusion mismatch and adult respiratory distress syndrome), heart (systolic and diastolic dysfunction), pancreas (pancreatitis), eyes (retinal problems including detachment), small and large intestines (ischemia), endocrine organs (adrenal glands, thyroid, and parathyroid), and immune system (exaggerated intravascular inflammation and changes in B and T cells as well as in T regulatory cells).

**An Atypical Form of Preeclampsia: Hemolysis, Elevated Liver Enzymes, and Low Platelet Syndrome**

Clinicians and investigators realized that “toxemia of pregnancy” could occur
without hypertension. For example, approximately 15% of patients with HELLP syndrome have normal diastolic blood pressure at admission, and 10% to 15% of patients with eclampsia do not develop hypertension. Goodlin emphasized this point with a case series of patients with atypical presentation and proposed that preeclampsia was another “great imitator” (others include syphilis, tuberculosis, and Lyme disease) (Figure 9). In 1982, Louis Weinstein coined the term “HELLP syndrome” to describe the combination of hemolysis, elevated liver enzymes, and low platelet count and proposed it to be a severe consequence of hypertension in pregnancy (Figure 10). However, this cluster of laboratory findings, often associated with abdominal pain, can occur in the absence of hypertension and proteinuria: sometimes, thrombocytopenia and liver dysfunction can resolve before delivery. Thrombocytopenia and an elevated SGOT (serum glutamic-oxaloacetic transaminase) level are independent risk factors for adverse pregnancy outcome after adjusting for hypertension and proteinuria: sometimes, thrombocytopenia and liver dysfunction can resolve before delivery. Thrombocytopenia and an elevated SGOT (serum glutamic-oxaloacetic transaminase) level are independent risk factors for adverse pregnancy outcome after adjusting for hypertension and proteinuria.

### Preeclampsia Without Proteinuria?

Proteinuria has been a requirement for the diagnosis of preeclampsia for decades, as it reflects renal involvement; however, in the 1990s, several groups of investigators began to question whether proteinuria should be a necessary criterion. Multiple studies reported that patients with severe gestational hypertension had a high rate of adverse pregnancy outcome, despite the absence of proteinuria. The frequency of preterm birth, SGA, placental abruption, neonatal respiratory distress syndrome, and perinatal death is higher among women with severe gestational hypertension than in those with mild preeclampsia. Additionally, approximately 50% of women with an initial diagnosis of gestational hypertension will subsequently develop proteinuria or end-organ damage. Two additional arguments favored abandoning the requirement of proteinuria for

<table>
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<th>Gestational ages, (wk)</th>
<th>Diastolic blood pressure (mm Hg)</th>
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<td>7.1</td>
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<td>1.0</td>
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<td>8.8</td>
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<td>1.0</td>
<td>1.2</td>
<td>1.8</td>
<td>2.8</td>
<td>-</td>
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<td>39–41</td>
<td>15,797</td>
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<td>1.0</td>
<td>1.0</td>
<td>1.2</td>
<td>3.2</td>
<td>2.6</td>
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Modified from Friedman and Neff

the diagnosis of preeclampsia: the standard definition (≥300 mg in a 24-hour urine collection or a ≥0.3 protein-to-creatinine ratio) is based on limited data,99,100 and dipstick testing for proteinuria is unreliable.101,102 Collectively, this set of observations, coupled with the lack of difference in the clinical management of gestational hypertension and conventionally defined preeclampsia, led the ACOG Task Force on Hypertension in Pregnancy to modify the definition of preeclampsia in 2013 as follows103: hypertension that develops after 20 weeks of gestation with proteinuria or evidence of end-organ damage, such as an abnormal renal function test, an elevation of liver enzymes, or thrombocytopenia without proteinuria. The modification reflected consensus that the crucial factor was blood pressure coupled with other manifestations of end-organ damage, one of which could be renal involvement. Although this recommendation was aimed at optimizing clinical management of patients, it has also led to an increase in the frequency of diagnoses of preeclampsia. It is unclear whether this change in diagnostic criteria will translate into improved maternal and perinatal outcomes because most of the newly diagnosed cases have a mild form of the disease.104 A more objective definition of preeclampsia is required to supersede the current approach of relying largely on blood pressure measurement. The identification of biomarkers for the early detection of the different forms of the syndrome will be crucial for improved diagnosis, taxonomy, prediction, and prevention.

**Antiangiogenic factors in preeclampsia**

The discovery that the placenta from patients with preeclampsia overexpressed mRNA and protein for sFlt-1, an antiangiogenic factor, was a breakthrough.105,106 The experiment consisted of a comparison of the transcriptomes of placentas from patients with and without preeclampsia. Karumanchi’s group found that two antiangiogenic factors—sFlt-1 and soluble endoglin (sEng)—were

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**TABLE 2**

<table>
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<tr>
<th>Proteinuria</th>
<th>Fetal mortality rate, %</th>
<th>Fetal mortality rate ratio</th>
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<tr>
<td>None (reference)</td>
<td>0.9</td>
<td>1.0</td>
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<tr>
<td>Trace</td>
<td>0.9</td>
<td>1.0</td>
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<tr>
<td>1+</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>2+</td>
<td>2.3</td>
<td>2.6</td>
</tr>
<tr>
<td>3+</td>
<td>4.4</td>
<td>4.9</td>
</tr>
<tr>
<td>4+</td>
<td>5.7</td>
<td>6.3</td>
</tr>
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Modified from Friedman and Neff.26


**FIGURE 7**

The synergistic effect of diastolic blood pressure and proteinuria on the risk of fetal death

The synergistic effect of diastolic blood pressure and proteinuria is evident, and it determines a considerable increase in the risk of fetal mortality. Modified from Friedman and Neff.26

overexpressed in the placentas of women with preeclampsia.106–109 Around the same time, it became known that the blockade of angiogenesis with vascular endothelial growth factor (VEGF) antagonists (monoclonal antibodies against VEGF) in nonpregnant patients with cancer would lead to hypertension and proteinuria.110 Encouraged by this finding, the investigators pursued a systematic series of studies that demonstrated that overproduction of sFlt-1 in pregnant animals recapitulated the features of preeclampsia and renal lesions associated with this condition (glomerular endotheliosis).106,111 This information, coupled with previous observations in patients with a low maternal serum concentration of the angiogenic factor—placental growth factor (PlGF)—strengthened the case for a role of an antiangiogenic imbalance in pre eclampsia. The antiangiogenic factor, endoglin, is also elevated in patients with preeclampsia and may explain why a subset of patients develop HELLP syndrome (Figure 11).112

The realization that antiangiogenic factors are linked to preeclampsia has improved the understanding of the pathophysiology and has allowed classification according to the presence or absence of an abnormal antiangiogenic profile. Antiangiogenic factors meet the criteria to be one, if not the major, “toxin” responsible for preeclampsia and eclampsia. The scientific basis for this claim is provided in companion articles in this Supplement.113,114

### The syndromic nature of preeclampsia

Obstetrical disorders, by contrast with diseases in the nonpregnant state, develop in the context of a unique biological situation—two individuals with different genomes coexisting, one inside the other. The common interest of the mother and her fetus is successful reproduction; however, conflict can occur when the interests of the mother and the fetus diverge, perhaps as the result of an insult (such as an infection or a compromised blood supply). The term “great obstetrical syndromes” was coined to describe the unique nature of obstetrical diseases. These features include (1) multiple etiologies, (2) a long subclinical phase, (3) fetal involvement, (4) the adaptive nature of clinical manifestations, and (5) complex gene-environment interactions.115–117 This section summarizes the evidence that preeclampsia has many of these features.

**Multiple etiologies**

Preeclampsia is not one disorder but rather different entities recognized by a common phenotype. Maternal, fetal, and placental causes of preeclampsia have been identified. The causative risk factors, or etiologies, of preeclampsia are reviewed in detail by Jung et al.118

**Long subclinical phase**

Although preeclampsia is diagnosed typically in the late second or third trimester, there is evidence of a pathologic process weeks or months before the diagnosis. Some women have an abnormal pressor response to angiotensin II,119 an abnormal uterine artery Doppler velocimetry measurement, or abnormal angiogenic and antiangiogenic profiles well before the clinical diagnosis.108,120–124

**Fetal involvement**

The diagnosis of the syndrome depends exclusively on maternal signs. Nonetheless, fetal involvement, typically in the form of growth restriction, is present in a subset of patients, and sometimes fetal growth deceleration precedes the diagnosis of preeclampsia. Other subtle hematological abnormalities such as thrombocytopenia and neutropenia have also been reported.125 Remarkably, some neonates born to mothers with preeclampsia have been noted to have dilatation of the right coronary artery and to be at risk for developing long-term cardiovascular disease as well as attention deficit and hyperactivity disorders.125,126

**Clinical manifestations are adaptive**

Hypertension can be considered an adaptive response generated by an injured placenta, which signals to the mother the need to maintain perfusion; this is accomplished by increasing maternal cardiac output, by an elevation of maternal blood pressure, or, in some cases, by a combination of both. That hypertension is an adaptive response is supported by a set of clinical observations including the resolution of maternal hypertension following the death of a growth-restricted fetus in a twin pregnancy,127–130 after SARS-CoV-2 infection,131 or after transfusion to correct fetal anemia with fetal parvovirus infection.132 Notably, pharmacologic treatment of maternal hypertension does not improve fetal outcomes. In some cases, the adaptive responses can become maladaptive, and

<table>
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<td>Rate ratios for fetal mortality by diastolic blood pressure and proteinuria combination</td>
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<table>
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<th>Diastolic pressure (mm Hg)</th>
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<tr>
<td>95–104</td>
<td>3.2</td>
</tr>
<tr>
<td>≥105</td>
<td>3.3</td>
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Modified from Friedman and Nett.25

*Reference rate of fetal mortality: 0.6% or 6 per 1000 births.

a hypertensive crisis can result in cerebrovascular accidents, liver rupture, and maternal death.

**Complex gene-environment interaction**

The occurrence of preeclampsia is likely influenced by a combination of genetic and environmental factors. A genetic predisposition has been suspected because preeclampsia clusters in families. Although most genetic association studies have focused on mothers, an association between a fetal DNA variant and the syndrome has been recently reported. Indeed, a fetal genome DNA variant near FLT1 (the gene encoding sFlt-1) is associated with the risk of preeclampsia. In addition to the potential contributions of fetal and maternal DNA variants to a particular obstetrical syndrome, the interaction and incompatibility of genotypes may also confer risk (e.g., specific combinations of major histocompatibility complex, class I, C (HLA-C) genotypes in the fetus and killer-cell immunoglobulin-like receptors in the mother and increased risk of other combinations of DNA variants in the genes encoding for the von Willebrand factor, alpha-2 chain of type IV collagen [COL4A2], and lymphotoxin alpha).

**Implications**

Considering preeclampsia as one of the great obstetrical syndromes has several consequences. Given that preeclampsia has multiple etiologies, it is unlikely that there will be a single diagnostic or prognostic test, treatment, or preventive strategy.

The long subclinical phase creates a window of opportunity for prediction and prevention, which have been accomplished with assessment in the first trimester and with the administration of aspirin. Early evidence suggests that prediction and prevention may also be possible for late-onset preeclampsia, but this may require different biomarkers, and serial testing and interventions (e.g., induction of labor).
Classification: Early vs Late, Mild vs Severe Disease

Preeclampsia has been classified according to gestational age at the time of diagnosis or delivery as early onset (<34 weeks) or late onset (≥34 weeks). Although other gestational-age cutoff values have been proposed, 34 weeks remains the most commonly used, likely because the rate of neonatal morbidities declines considerably after this gestational age. Specifically, in women with severe preeclampsia, expectant management is not considered, and induction of labor is recommended after 34 weeks of gestation. In addition, preeclampsia can be classified according to its severity (Table 4).103,145

Multiple lines of evidence have now coalesced, proposing that early and late preeclampsia are different conditions (Table 5). Early-onset preeclampsia is characterized by a higher frequency of HELLP syndrome,142,147 abnormal uterine artery Doppler waveforms,142 atherosis,148,149 placental lesions consistent with maternal vascular malperfusion,142,150 SGA,141,142,155 and fetal growth restriction.142 Moreover, abnormal maternal plasma ratios of PI GF-to-sFLT-1 or PI GF-to-sEng are present in 80% to 90% of patients with early-onset preeclampsia, but in only 40% to 50% of patients with late-onset preeclampsia.141 Early-onset preeclampsia can be considered a clinical manifestation of atherosclerosis in pregnancy while late-onset disease is a metabolic crisis emerging from a mismatch between fetal demands and maternal supply.

Postpartum Preeclampsia

This condition has been an enigma as delivery of the placenta is considered to be the cure of preeclampsia. Retained fragments of the placenta have been implicated in postpartum preeclampsia and eclampsia for decades. In 1960, while investigating the etiology of hypertension in “toxemia of pregnancy,” Hunter and Howard20 reported that the decidua of patients with toxemia and molar pregnancy produced a pressor substance: “hysterotonin.” Although the molecule responsible for this pressor response was never characterized, Hunter et al154 proposed that postpartum curettage of the decidua could improve the condition. Indeed, curettage was reported to ameliorate hypertension in 69 patients. In one patient with postpartum eclampsia, convulsions did not recur after curettage (Figure 12).154 Approximately 30 years later, Magann et al155 reported the results of a randomized clinical trial of immediate postpartum curettage in 32 patients with severe preeclampsia and observed that patients who had undergone curettage had significantly lower blood pressure...
FIGURE 11
The role of sFlt-1 in preeclampsia

A Normal Pregnancy

B Preeclampsia

A, Remodeling of the spiral arteries increases blood supply to the fetus. B, In preeclampsia, sFlt-1 is overexpressed in the placenta, leading to hypertension and proteinuria. Modified from Luttun et al.155

PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; VEGF, vascular endothelial growth factor.


(Figure 13, A) as well as a significantly higher urinary output and platelet count (Figure 13, B) than those who did not undergo a curettage. Collectively, these observations suggest that material present in the uterus after the delivery of the placenta can still have biological properties. Although Hunter et al154 attributed this to the decidua, trophoblasts are also present in the uterus after delivery of the placenta and are consistently observed in histologic examinations of hysterectomy specimens. Therefore, it is possible that trophoblasts may continue to be a source of bioactive material. Why some patients develop hypertension and proteinuria only after delivery remains an unanswered question.

Postpartum preeclampsia belongs to a group of conditions of unknown etiology diagnosed after delivery that include cardiomyopathy, renal failure, uremic hemolytic syndrome, and acute fatty liver. Insights into the pathophysiology of these conditions can be gleaned by recent progress made in the understanding of peripartum cardiomyopathy, which is now recognized as the result of the antiangiogenic factor sFlt-1 in a two-hit model.156 The first is an increased concentration of sFlt-1 in the maternal circulation, which can impair cardiac function, and the second is a lack of local proangiogenic defenses in the maternal heart. Peripartum cardiomyopathy can be experimentally induced in pregnant mice by the combination of increased sFlt-1 (through an adenovirus vector) and gene deletion of a regulator of angiogenesis called “peroxisome proliferator-activated receptor gamma.
Similiarly, pregnant women with preeclampsia have impaired subclinical renal function and proteinuria after delivery, which may persist for months. The antepartum sFlt-1 concentration correlates with a lower glomerular filtration rate, and a high concentration is a risk factor for renal impairment at six and 12 months postpartum. Recent observations suggest that the pathophysiology of acute fatty liver of pregnancy may also be related to an excessive concentration of sFlt-1 (Figure 14). Why and how an excess of sFlt-1 or other antiangiogenic factors may target the heart, kidney, liver, or brain (in some cases of postpartum eclampsia) are unknown. We believe that several enigmatic postpartum syndromes represent the clinical manifestations of vascular dysfunction in the peripartum period.

Vascular Dysfunction of Pregnancy: Unmasked, Induced, Protean

The most important adaptation for a successful pregnancy is the establishment and development of an adequate blood supply to the placenta and conceptus. The clinical consequences of suboptimal perfusion range from fetal growth restriction, SGA, preeclampsia, abruptio placenta, and fetal death (Figure 15). A fundamental question is: why does maternal malperfusion lead to one particular syndrome rather than to another?
others? The timing and magnitude of the insult and the genetic makeup of the mother, fetus, and placenta are likely to determine the clinical presentation. Extreme compromise of the blood supply results in fetal death. Lesser degrees of maternal malperfusion could be compensated by a reduction in fetal growth, maternal hypertension, or a combination of both. In some cases, the adaptive response may be spontaneous preterm birth. Why some cases of fetal growth restriction attributable to placental malperfusion are associated with preeclampsia and others are not is unknown.

It is now clear that a subset of women who develop preeclampsia have preexisting vascular dysfunction, which manifests clinically during pregnancy and remains operative in the postpartum period. This realization offers unique opportunities to improve the healthcare of women by implementing strategies to prevent cardiovascular disease. Figure 16 illustrates the long-term adverse events associated with preeclampsia. These include not only maternal hypertension and coronary artery disease but also vascular dementia and end-stage renal disease. This article has focused on preeclampsia. However, patients with other complications of pregnancy, such as fetal death, are also at risk of subsequent cardiovascular diseases. Therefore, vascular dysfunction during pregnancy diagnosed through preeclampsia or other great obstetrical syndromes has important implications for women’s health.

**Conclusion**
The implications of preeclampsia in maternal and infant health have been a

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**FIGURE 12**
Effect of uterine curettage on blood pressure in a woman with postpartum eclampsia


**FIGURE 13**
Effects of uterine curettage in patients with preeclampsia

Postpartum uterine curettage has an effect not only on blood pressure (A) but also on platelet count (B) in patients with preeclampsia. Modified from Magann et al. Erez. Conceptual evolution of preeclampsia and eclampsia as a syndrome. Am J Obstet Gynecol 2022.
major determinant in the organization of prenatal care for more than a century. Initially thought to be a disorder of the central nervous system, and then to involve the kidneys, it is now considered fundamentally a cardiovascular disorder. The view that preeclampsia is a pregnancy-specific condition caused by the placenta and cured only by delivery, has been the accepted dogma. We now know that vascular dysfunction, clinically recognized by the combination of hypertension and proteinuria, is not specific to pregnancy; it can occur in non-pregnant subjects after a viral infection such as SARS-CoV-2, the administration of VEGF inhibitors, or in the context of other disorders such as diabetes. What makes pregnant women particularly prone to develop vascular dysfunction is the placenta, an organ that produces antiangiogenic factors in response to insults. However, it is not clear if all cases of preeclampsia require placental involvement. The notion that preeclampsia can be cured only by delivery also needs to be revisited. Indeed, hypertension and proteinuria in pregnant women with SARS-CoV-2 infection can disappear after the viral infection is cleared. Moreover, preeclampsia can resolve in twin gestations with selective fetal growth restriction after the death of...

**FIGURE 14**

**Plasma concentration of sFlt-1 in women with normal pregnancy, preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy**

Women with acute fatty liver of pregnancy have a higher plasma concentration of sFlt-1 than women with other conditions. Data are presented as individual values (dot) and median (bar). Modified from Neuman et al. 

**FIGURE 15**

**Vascular dysfunction of pregnancy can lead to the great obstetrical syndromes**

Vascular dysfunction during pregnancy may result in one of several obstetrical syndromes. The timing and magnitude of the insult may determine the clinical syndromes.

PROM, premature rupture of membranes.

the affected twin or after treatment of fetal anemia caused by parvovirus B19 infection. These clinical observations about the reversibility of preeclampsia are buttressed by experimental evidence that the molecular abnormalities of trophoblasts obtained from patients with preeclampsia can resolve in vitro. Perhaps, it is time to reframe our conceptualization of preeclampsia. Has too much weight been given to the results of a sphygmomanometer to identify this complex syndrome? The identification of biological markers that detect the pathophysiologic derangements of this syndrome in early pregnancy, or even before, is necessary to the diagnosis, classification, treatment, prediction, and prevention of this elusive disorder.

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