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CHAPTER 40: Hypertensive Disorders

An eclamptic convulsion sometimes occurs without warning, "like a bolt from a clear sky", in women who are apparently in perfect health. In the majority of cases, however, the outbreak is preceded for a longer or shorter period by premonitory symptoms indicative of toxemia of pregnancy, among the more common being oedema, headache, epigastric pain, and possibly disturbances of vision.

—J. Whitridge Williams (1903)

INTRODUCTION

At the time of this textbook's first edition, it was accepted that "toxemia" preceded most cases of eclampsia. The central role of hypertension had not yet been discovered, and after many years, it became apparent that preeclampsia was a syndrome of which hypertension was only one important facet. Still, the mechanisms by which pregnancy incites or aggravates hypertension remain unsolved. Indeed, hypertensive disorders remain among the most significant and intriguing unsolved problems in obstetrics. These disorders complicate 5 to 10 percent of all pregnancies, and together they are one of the deadly triad—along with hemorrhage and infection—that contributes greatly to maternal morbidity and mortality rates. Of hypertensive disorders, the *preeclampsia syndrome*, either alone or superimposed on chronic hypertension, is the most dangerous. As subsequently discussed, new-onset hypertension during pregnancy—termed *gestational hypertension*—is followed by signs and symptoms of preeclampsia almost half the time, and preeclampsia is identified in 4 to 5 percent of all pregnancies (Martin, 2012).

The World Health Organization (WHO) systematically reviews maternal mortality worldwide, and in developed countries, 16 percent of maternal deaths were attributed to hypertensive disorders (Khan, 2006). In the United States from 2011 to 2013, 7.4 percent of 2009 pregnancy-related maternal deaths were caused by preeclampsia or eclampsia (Creanga, 2017). A similar rate was 10 percent in France from 2003 through 2007 (Saucedo, 2013). Importantly, more than half of these hypertension-related deaths were deemed preventable (Berg, 2005).

TERMINOLOGY AND DIAGNOSIS

To update and codify the terminology and classification of hypertensive disorders of pregnancy, a Task Force of the American College of Obstetricians and Gynecologists (2013) has provided evidence-based recommendations for clinical practice. The previous basic classification was retained and describes four types of hypertensive disease:

1. Preeclampsia and eclampsia syndrome
2. Chronic hypertension of any etiology
3. Preeclampsia superimposed on chronic hypertension
4. Gestational hypertension—definitive evidence for the preeclampsia syndrome does not develop and hypertension resolves by 12 weeks postpartum.

Importantly, this classification differentiates the preeclampsia syndrome from other hypertensive disorders because it is potentially more ominous.

Diagnosis of Hypertensive Disorders

Hypertension is diagnosed empirically when appropriately taken blood pressure exceeds 140 mm Hg systolic or 90 mm Hg diastolic. Korotkoff phase V is used to define diastolic pressure. Previously, incremental increases of 30 mm Hg systolic or 15 mm Hg diastolic above blood pressure values taken at midpregnancy had also been used as diagnostic criteria, even when absolute values were <140/90 mm Hg. These incremental changes are no longer used to define hypertension, but it is recommended that such women be observed more closely because eclamptic seizures develop in some whose

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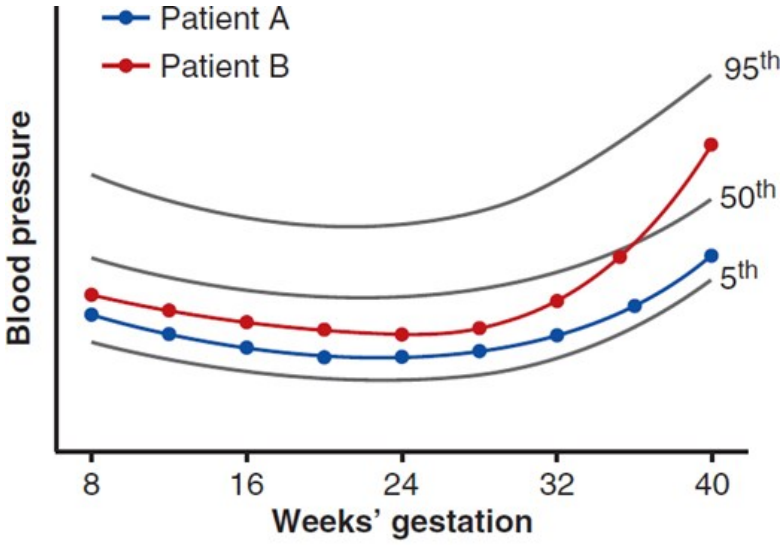
blood pressures have stayed below 140/90 mm Hg (Alexander, 2006). Also, a sudden rise in mean arterial pressure but still in a normal range—"delta hypertension"—may signify preeclampsia (Macdonald-Wallis, 2012; Zeeman, 2007).

Concept of "Delta Hypertension"

The systolic and diastolic blood pressure levels of 140/90 mm Hg have been arbitrarily used since the 1950s to define "hypertension" in nonpregnant individuals. However, these levels were selected by insurance companies to characterize a group of middle-aged men. It seems more realistic to define normal-range blood pressures that fall between an upper and lower limit for a particular population—such as young, healthy, pregnant women. A schematic example using arbitrary mean arterial blood pressure readings is shown in Figure 40-1. Data curves for both women show blood pressure measurements near the 25th percentile until 32 weeks. These begin to rise in patient B, who by term has substantively higher blood pressures. However, her pressures are still <140/90 mm Hg, and thus she is considered to be "normotensive." We use the term *delta hypertension* to describe this rather acute rise in blood pressure. Some of these women will go on to have obvious preeclampsia, and some even develop eclamptic seizures or HELLP (hemolysis, elevated liver enzyme levels, low platelet count) syndrome while still normotensive.

FIGURE 40-1

Schematic shows normal reference ranges for mean arterial blood pressure changes across pregnancy. Patient A (*blue*) has mean blood pressures near the 20th percentile throughout pregnancy. Patient B (*red*) has a similar pattern with mean pressures at the 25th percentile until approximately 36 weeks when her blood pressure begins to rise. By term, it is substantively higher and in the 75th percentile, but she is still considered "normotensive."



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Gestational Hypertension

This diagnosis is made in women whose blood pressures reach 140/90 mm Hg or greater for the first time after midpregnancy, but in whom *proteinuria is not identified.* Almost half of these women subsequently develop preeclampsia syndrome. Even so, when blood pressure increases appreciably, it is dangerous to both mother and fetus to ignore this rise only because proteinuria has not yet developed. As Chesley (1985) emphasized, 10 percent of eclamptic seizures develop before overt proteinuria can be detected. Finally, gestational hypertension is reclassified by some as *transient hypertension* if evidence for preeclampsia does not develop and the blood pressure returns to normal by 12 weeks postpartum.

Preeclampsia Syndrome

Preeclampsia is best described as a pregnancy-specific syndrome that can affect virtually every organ system. In addition, it heralds a higher incidence of cardiovascular disease later in life (Long-Term Consequences). Although preeclampsia is much more than simply gestational hypertension with proteinuria, appearance of proteinuria remains an important diagnostic criterion. Thus, proteinuria is an *objective* marker and reflects the system-

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wide endothelial leak that characterizes the preeclampsia syndrome.

In some women with the preeclampsia syndrome, neither overt proteinuria nor fetal-growth restriction are features (Sibai, 2009). Because of this, the Task Force (2013) suggests other diagnostic criteria, which are shown in Table 40-1. Evidence of multiorgan involvement may include thrombocytopenia, renal dysfunction, hepatocellular necrosis, central nervous system perturbations, or pulmonary edema.

TABLE 40-1

Classification and Diagnosis of Pregnancy-Associated Hypertension

Condition	Criteria Required
Gestational hypertension	BP >140/90 mm Hg after 20 weeks in previously normotensive women
Preeclampsia: Hypertension plus	
Proteinuria	• ≥300 mg/24 h, or • Urine protein: creatinine ratio ≥0.3, or • Dipstick 1+ persistent[a]
or	
Thrombocytopenia	• Platelet count <100,000/**µL**
Renal insufficiency	• Creatinine level >1.1 mg/dL or doubling of baseline[b]
Liver involvement Cerebral symptoms	• Serum transaminase levels[c] twice normal • Headache, visual disturbances, convulsions
Pulmonary edema	—

[a]Recommended only if sole available test.

[b]No prior renal disease.

[c]AST (aspartate transaminase) or ALT (alanine transaminase).

BP = blood pressure.

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Indicators of Preeclampsia Severity

The markers listed in Table 40-1 are also used to classify preeclampsia syndrome severity. Although many use a dichotomous "mild" and "severe" classification, the Task Force (2013) discourages the use of "mild preeclampsia." It is problematic that there are criteria for the diagnosis of "severe" preeclampsia, but the default classification is either implied or specifically termed as "mild," "less severe," or "nonsevere" (Alexander, 2003; Lindheimer, 2008b). There are no generally agreed-on criteria for "moderate" preeclampsia—an elusive third category. We use the criteria listed in

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Table 40-2, which are categorized as “severe” versus “nonsevere.”

TABLE 40-2

Indicators of Severity of Gestational Hypertensive Disorders[a]

Abnormality	Nonsevere[b]	Severe
Diastolic BP	<110 mm Hg	≥110 mm Hg
Systolic BP	<160 mm Hg	≥160 mm Hg
Proteinuria[c]	None to positive	None to positive
Headache	Absent	Present
Visual disturbances	Absent	Present
Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsion (eclampsia)	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia (<100,000/μL)	Absent	Present
Serum transaminase elevation	Minimal	Marked
Fetal-growth restriction	Absent	Present
Pulmonary edema	Absent	Present
Gestational age	Late	Early

[a]Compare with criteria in Table 40-1.

[b]Includes “mild” and “moderate” hypertension not specifically defined.

[c]Most disregard degrees of proteinuria to classify nonsevere or severe.

BP = blood pressure.

Some symptoms are considered ominous. *Headaches* or *visual disturbances* such as scotomata can precede *eclampsia*, which is a convulsion not attributable to another cause. The seizures are generalized and may appear before, during, or after labor. The proportion that develops seizures later, after 48 hours postpartum, approximates 10 percent (Sibai, 2005; Zwart, 2008). Another symptom, *epigastric or right upper quadrant pain*, frequently accompanies hepatocellular necrosis, ischemia, and edema that ostensibly stretches Glisson capsule. This characteristic pain is frequently accompanied by elevated serum hepatic transaminase levels. Finally, *thrombocytopenia* also signifies worsening preeclampsia. It represents platelet activation and aggregation as well as microangiopathic hemolysis. Other factors indicative of severe preeclampsia include renal or cardiac involvement, obvious fetal-growth restriction, and early-onset disease.

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The more profound these signs and symptoms, the less likely it is that they can be temporized, and the more likely that delivery will be required. *A caveat is that differentiation between nonsevere and severe gestational hypertension or preeclampsia can be misleading because what might be apparently mild disease may progress rapidly to severe disease.*

Preeclampsia Superimposed on Chronic Hypertension

Regardless of its cause, any chronic hypertensive disorder predisposes a woman to develop superimposed preeclampsia syndrome. Chronic underlying hypertension is diagnosed in women with documented blood pressures >140/90 mm Hg before pregnancy or before 20 weeks' gestation, or both. Hypertensive disorders can create difficult problems with diagnosis and management in women who are not first seen until after midpregnancy. This is because blood pressure normally drops during the second and early third trimesters in both normotensive and chronically hypertensive women (see Fig. 40-1). Thus, a woman with previously undiagnosed chronic vascular disease who is seen before 20 weeks frequently has blood pressures within normal range. During the third trimester, however, as blood pressures return to their originally hypertensive levels, it may be difficult to determine whether hypertension is chronic or induced by pregnancy. Even a careful search for evidence of preexisting end-organ damage may be futile, as many of these women have mild disease and no evidence of ventricular hypertrophy, retinal vascular changes, or renal dysfunction.

In some with chronic hypertension, blood pressure rises to obviously abnormal levels, typically after 24 weeks' gestation. If new-onset or worsening baseline hypertension is accompanied by new-onset proteinuria or other findings listed in Table 40-1, then superimposed preeclampsia is diagnosed. Compared with "pure" preeclampsia, superimposed preeclampsia commonly develops earlier in pregnancy. It also tends to be more severe and more often is accompanied by fetal-growth restriction. The same criteria shown in Table 40-2 are also used to further characterize severity of superimposed preeclampsia.

INCIDENCE AND RISK FACTORS

Young and nulliparous women are particularly vulnerable to developing preeclampsia, whereas older women are at greater risk for chronic hypertension with superimposed preeclampsia. The incidence is markedly influenced by race and ethnicity—and thus by genetic predisposition. In one study by the Maternal-Fetal Medicine Units (MFMU) Network, the incidence of preeclampsia was 5 percent in white, 9 percent in Hispanic, and 11 percent in African-American women (Myatt, 2012a,b). In addition, black women have greater morbidity (Shahul, 2015). In several worldwide studies reviewed by Staff and coworkers (2015), the incidence of preeclampsia in nulliparous populations ranged from 3 to 10 percent. The incidence of preeclampsia in multiparas also varies and ranges from 1.4 to 4 percent (Fisher, 2015).

Bartsch and associates (2016) extracted data from more than 25 million pregnancies and calculated relative risks for several clinical factors shown in Table 40-3. Others include the metabolic syndrome and hyperhomocysteinemia (Karumanchi, 2016a; Masoudian, 2016; Scholten, 2013). Pregnancies with a male fetus are also at slightly higher risk (Jaskolka, 2017). Although smoking during pregnancy causes various adverse pregnancy outcomes, ironically, it carries a *reduced risk* for hypertension during pregnancy (Bainbridge, 2005; Kraus, 2014). Other factors are human immunodeficiency virus (HIV) seropositivity and sleep-disordered breathing (Facco, 2017; Sansone, 2016).

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TABLE 40-3

Selected Clinical Risk Factors for Preeclampsia

Risk Factor	Pregnancies (millions)	Pooled Unadjusted Relative Risk (95% CI)
SLE	2.43	2.5 (1.0–6.3)
Nulliparity	2.98	2.1 (1.9–2.4)
Age >35	5.24	1.2 (1.1–1.3)
Prior stillbirth	0.063	2.4 (1.7–3.4)
CKD	0.97	1.8 (1.5–2.1)
ART	1.46	1.8 (1.6–2.1)
BMI >30	5.92	2.8 (2.6–3.1)
Multifetal	7.31	2.9 (2.6–3.1)
Prior abruption	0.29	2.0 (1.4–2.7)
Diabetes	2.55	3.7 (3.1–4.3)
Prior preeclampsia	3.72	8.4 (7.1–9.9)
CHTN	6.59	5.1 (4.0–6.5)
APA	0.22	2.8 (1.8–4.3)

APA = antiphospholipid antibody; ART = assisted reproductive technology; BMI = body mass index; CHTN = chronic hypertension; CKD = chronic kidney disease; SLE = systemic lupus erythematosus.

Data from Bartsch, 2016.

For eclampsia, the incidence has declined in areas where health care is more readily available. In the United States in 1998, it affected 1 in 3250 births (Ventura, 2000). Except for Iceland, which has an extremely low rate, in countries with adequate resources the incidence averages 1 in 2000 to 3000 deliveries (Andersgaard, 2006; Jaatinen, 2016; O'Connor, 2013; Royal College of Obstetricians and Gynaecologists, 2006; Zwart, 2008).

ETIOPATHOGENESIS

Any satisfactory theory concerning the origins of preeclampsia must account for the observation that gestational hypertensive disorders are more likely to develop in women with the following characteristics:

- Are exposed to chorionic villi for the first time
- Are exposed to a superabundance of chorionic villi, as with twins or hydatidiform mole
- Have preexisting conditions associated with endothelial cell activation or inflammation, such as diabetes, obesity, cardiovascular or renal disease, immunological disorders, or hereditary influences

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- Are genetically predisposed to hypertension developing during pregnancy.

A fetus is not a requisite for preeclampsia to develop. And, although chorionic villi are essential, they need not be intrauterine. For example, preeclampsia can develop with an abdominal pregnancy (Worley, 2008). *Regardless of precipitating etiology, the cascade of events leading to the preeclampsia syndrome is characterized by abnormalities that result in systemic vascular endothelial damage with resultant vasospasm, transudation of plasma, and ischemic and thrombotic sequelae.*

Phenotypic Expression of Preeclampsia Syndrome

The preeclampsia syndrome varies widely in its clinical phenotypic expression. But, at least two major subtypes are differentiated by whether or not remodeling of uterine spiral arterioles by endovascular trophoblasts is defective. This concept has given rise to the "two-stage disorder" theory of preeclampsia pathogenesis. According to Redman and coworkers (2015a), stage 1 is caused by faulty endovascular trophoblastic remodeling that downstream causes the stage 2 clinical syndrome. Importantly, stage 2 can be modified by preexisting maternal conditions that are also manifest by endothelial cell activation or inflammation and are listed in the third prior bullet.

Such staging is artificial, and it seems logical that preeclampsia syndrome presents clinically as a spectrum of worsening disease. Moreover, evidence is accruing that many "isoforms" exist as discussed subsequently. Examples include differences in maternal and fetal characteristics, placental findings, and early- versus late-onset disease (Phillips, 2010; Valensise, 2008; van der Merwe, 2010).

Etiology

An imposing number of mechanisms have been proposed to explain the cause of preeclampsia. Those currently considered important include:

1. Placental implantation with abnormal trophoblastic invasion of uterine vessels
2. Immunological maladaptive tolerance between maternal, paternal (placental), and fetal tissues
3. Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy
4. Genetic factors including inherited predisposing genes and epigenetic influences.

Abnormal Trophoblastic Invasion

Discussed in Chapter 5 (Blastocyst), normal implantation is characterized by extensive remodeling of the spiral arterioles within the decidua basalis (Fig. 40-2). Endovascular trophoblasts replace the vascular endothelial and muscular linings to enlarge the vessel diameter (Zhou, 1997). The veins are invaded only superficially.

FIGURE 40-2

Schematic representation of normal placental implantation shows proliferation of extravillous trophoblasts from an anchoring villus. These trophoblasts invade the decidua and extend into the walls of the spiral arteriole to replace the endothelium and muscular wall to create a dilated low-resistance vessel. With preeclampsia, defective implantation is characterized by incomplete invasion of the spiral arteriolar wall by extravillous trophoblasts. This results in a small-caliber vessel with high resistance to flow.

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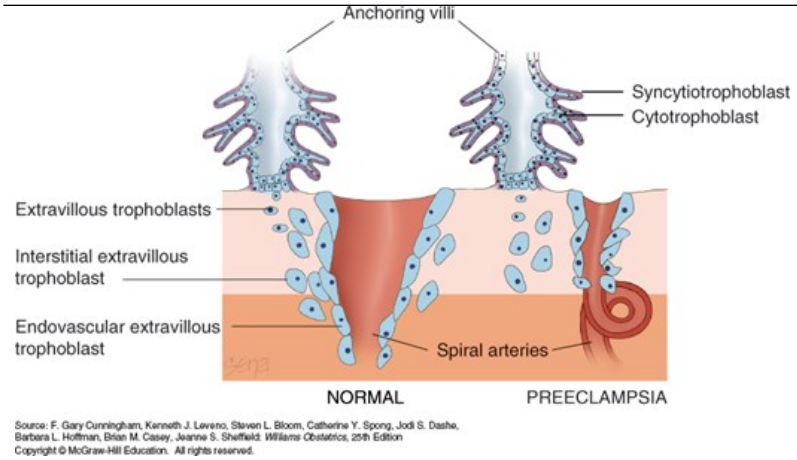

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In some cases of preeclampsia, however, trophoblastic invasion may be incomplete. With this, decidual vessels, but not myometrial vessels, become lined with endovascular trophoblasts. The deeper myometrial arterioles thus do not lose their endothelial lining and musculoelastic tissue, and their mean external diameter is only half that of corresponding vessels in normal placentas (Fisher, 2015). In general, the magnitude of defective trophoblastic invasion correlates with the severity of the hypertensive disorder (Madazli, 2000). And importantly, it is more prevalent in women with early-onset preeclampsia (Khodzhaeva, 2016). McMahon and associates (2014) found that lower levels of soluble antiangiogenic growth factors may be involved in this faulty endovascular remodeling.

From placental electron microscopy studies, early preeclamptic changes include endothelial damage, insudation of plasma constituents into vessel walls, proliferation of myointimal cells, and medial necrosis (De Wolf, 1980). Hertig (1945) referred to lipid accumulation in myointimal cells and macrophages as *atherosis*. These findings are more common in placentas from women diagnosed with preeclampsia before 34 weeks (Nelson, 2014b). Acute placental vascular atherosis may also identify a group of women at greater risk for later atherosclerosis and cardiovascular disease (Staff, 2015). In pregnancy, the abnormally narrow lumen of spiral arterioles likely impairs placental blood flow. Diminished perfusion and a hypoxic environment eventually lead to release of *placental debris* or *microparticles.*

At this point, these changes incite a systemic inflammatory response, which is stage 2 of the preeclampsia syndrome (Lee, 2012; Redman, 2012). Defective placentation is posited to further cause the susceptible woman to develop gestational hypertension, the preeclampsia syndrome, preterm delivery, a growth-restricted fetus, and/or placental abruption (Brosens, 2011; Labarrere, 2017; Nelson, 2014b).

Immunological Factors

Maternal immune tolerance to paternally derived placental and fetal antigens is discussed in Chapter 5 (Fetal–Maternal Interface). Loss of this tolerance is another cited theory for preeclampsia (Erlebacher, 2013). Certainly, the histological changes at the maternal-placental interface are suggestive of acute graft rejection.

Inferential data also suggest that preeclampsia is an immune-mediated disorder. For example, the risk of preeclampsia is appreciably enhanced in circumstances in which formation of blocking antibodies to placental antigenic sites *might* be impaired. In this scenario, the first pregnancy would carry a higher risk. Tolerance dysregulation might also explain an elevated risk when the paternal antigenic load is increased, that is, with two sets of paternal chromosomes—a "double dose." Namely, women with molar pregnancies have a high incidence of early-onset preeclampsia. Women with a trisomy 13 fetus also have a 30- to 40-percent incidence of preeclampsia. These women have elevated serum levels of antiangiogenic factors. The gene for one of these factors, *soluble fms-like tyrosine kinase 1*, is on chromosome 13 (Bdolah, 2006). Conversely, women previously exposed to paternal antigens, such as a prior pregnancy with the *same* partner, are "immunized" against preeclampsia. This phenomenon is not as apparent in women with a prior abortion (Strickland, 1986). Multiparas impregnated by a new consort have a greater risk of preeclampsia (Mostello, 2002).

Redman and colleagues (2015a) reviewed the possible role of *immune maladaptation* in preeclampsia pathophysiology. In women destined to be preeclamptic, extravillous trophoblasts early in pregnancy express reduced amounts of immunosuppressive nonclassic human leukocyte antigen G (HLA G). Black women more commonly have the 1597ΔC gene allele that further predisposes to preeclampsia (Loisel, 2013). These changes may contribute to the defective placental vascularization in stage 1 of the preeclampsia syndrome. As discussed in Chapter 4 (Leukocytes and Lymphocytes), T-helper (Th) lymphocytes during normal pregnancy are produced so that type 2 activity is increased in relation to type 1—so-called

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type 2 bias (Redman, 2012, 2015a). Th2 cells promote humoral immunity, whereas Th1 cells stimulate inflammatory cytokine secretion. Beginning in the early second trimester in women who develop preeclampsia, Th1 action is increased.

Endothelial Cell Activation

Inflammatory changes are believed to be a continuation of stage 1 alterations. In response to ischemia or other inciting causes, placental factors are released and begin a cascade of events (Davidge, 2015). Thus, antiangiogenic and metabolic factors and other inflammatory leukocyte mediators are thought to provoke systemic endothelial cell injury, which is used synonymously here with *endothelial cell activation* or *dysfunction*.

Endothelial cell dysfunction may result from an extreme activated state of leukocytes in the maternal circulation (Faas, 2000; Gervasi, 2001). Briefly, cytokines such as tumor necrosis factor-α (TNF-α) and the interleukins may contribute to the systemic oxidative stress associated with preeclampsia. This is characterized by reactive oxygen species and free radicals that lead to formation of self-propagating lipid peroxides (Manten, 2005). These peroxides in turn generate highly toxic radicals that injure systemic vascular endothelial cells, modify nitric oxide production by these cells, and interfere with prostaglandin balance. Other consequences of oxidative stress include production of the lipid-laden macrophage foam cells seen in placental atherosis, activation of systemic microvascular coagulation manifested by thrombocytopenia, and greater systemic capillary permeability reflected by edema and proteinuria.

Genetic Factors

Preeclampsia appears to be a multifactorial, polygenic disorder. In one study of almost 1.2 million Swedish births, a genetic association for gestational hypertension and for preeclampsia was found (Nilsson, 2004). Ward and Taylor (2015) cite an incident risk for preeclampsia of 20 to 40 percent for daughters of preeclamptic mothers; 11 to 37 percent for sisters of preeclamptic women; and 22 to 47 percent for twins. Ethnoracial factors are important, as evidenced by the high incidence of preeclampsia in African-American women. It may be that Latina women have a lower incidence because of interactions of American Indian and white race genes (Shahabi, 2013).

The hereditary predisposition for preeclampsia likely stems from interactions of literally hundreds of inherited genes—both maternal and paternal—that control myriad enzymatic and metabolic functions throughout every organ system (Triche, 2014). Plasma-derived factors may induce some of these genes in preeclampsia (Mackenzie, 2012). Thus, the clinical manifestation in any given woman with the preeclampsia syndrome will occupy a spectrum. In this regard, phenotypic expression will differ among similar genotypes depending on interactions with environmental components (Yang, 2013).

Hundreds of genes have been studied for their possible association with preeclampsia (Buurma, 2013; Sakowicz, 2016; Ward, 2015). Several that may have a significant association with the syndrome are listed in Table 40-4. However, because of the complex phenotypic expression of preeclampsia, it is doubtful that any *one* candidate gene will be found responsible. Indeed, Majander and associates (2013) have linked preeclampsia predisposition to even *fetal* genes on chromosome 18.

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TABLE 40-4

Genes with Possible Associations with Preeclampsia Syndrome

Gene (Polymorphism)	Function Affected
MTHFR (C677T)	Methylene tetrahydrofolate reductase
F5 (Leiden)	Factor V_{Leiden}
AGT (M235T)	Angiotensinogen
HLA (Various)	Human leukocyte antigens
NOS3 (Glu 298 Asp)	Endothelial nitric oxide
F2 (G20210A)	Prothrombin (factor II)
ACE (I/DatIntron 16)	Angiotensin-converting enzyme
CTLA4	Cytotoxic T-lymphocyte-associated protein
LPL	Lipoprotein lipase
SERPINE1	Serine peptidase inhibitor
GNA promoter	Decreased methylation

Data from Buurma, 2013; Staines-Urias, 2012; Triche, 2014; Ward, 2014; Ye, 2016.

Pathogenesis

Vasospasm

The concept of vasospasm with preeclampsia has been advanced for a century (Volhard, 1918). Systemic endothelial activation causes vasospasm that elevates resistance to produce subsequent hypertension. Concurrently, systemic endothelial cell injury promotes interstitial leakage, and blood constituents, including platelets and fibrinogen, are deposited subendothelially. Endothelial junctional proteins are also disrupted, and the subendothelial region of resistance arteries undergoes ultrastructural change (Suzuki, 2003; Wang, 2002). The much larger venous circuit is similarly involved.

With diminished blood flow because of maldistribution from vasospasm and interstitial leakage, ischemia of the surrounding tissues can lead to necrosis, hemorrhage, and other end-organ disturbances characteristic of the syndrome. One important clinical correlate to this is the markedly attenuated blood volume seen in women with severe preeclampsia (Zeeman, 2009).

Endothelial Cell Injury

Injury to systemic endothelial cells is now a centerpiece of preeclampsia pathogenesis (Davidge, 2015). In this scheme, protein factor(s)—likely placental—are secreted into the maternal circulation and provoke activation and dysfunction of the systemic vascular endothelium. Many facets of the clinical syndrome of preeclampsia are thought to result from these widespread endothelial cell changes.

Intact endothelium has anticoagulant properties. Also, systemic endothelial cells, by releasing nitric oxide, blunt the response of vascular smooth

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muscle to agonists. Injured or activated endothelial cells may produce less nitric oxide and may secrete substances that promote coagulation and greater sensitivity to vasopressors. Further evidence of endothelial activation includes the characteristic changes in glomerular capillary endothelial morphology, greater capillary permeability, and elevated blood concentrations of substances associated with endothelial activation. Likely, multiple factors in the plasma of preeclamptic women combine to exert these vasoactive effects (Myers, 2007; Walsh, 2009).

Increased Pressor Responses

As discussed in Chapter 4 (Renin, Angiotensin II, and Plasma Volume), pregnant women normally develop refractoriness to infused vasopressors (Abdul-Karim, 1961). Women with early preeclampsia, however, have enhanced vascular reactivity to infused norepinephrine and angiotensin II (Raab, 1956; Talledo, 1968). Moreover, increased sensitivity to angiotensin II clearly precedes the onset of gestational hypertension (Gant, 1974). Paradoxically, women who develop preterm preeclampsia have lower circulating levels of angiotensin II (Chase, 2017).

Several prostaglandins are thought to be central to preeclampsia syndrome pathophysiology. Specifically, the blunted pressor response seen in normal pregnancy is at least partially due to diminished vascular responsiveness mediated by endothelial prostaglandin synthesis. For example, compared with normal pregnancy, endothelial prostacyclin (PGI_2) production is lower in preeclampsia. This action appears to be mediated by phospholipase A_2 (Davidge, 2015). At the same time, thromboxane A_2 secretion by platelets is increased, and the prostacyclin:thromboxane A_2 ratio declines. The net result favors greater sensitivity to infused angiotensin II and, ultimately, vasoconstriction (Spitz, 1988). These changes are apparent as early as 22 weeks' gestation in gravidas who later develop preeclampsia (Chavarria, 2003).

Nitric oxide is a potent vasodilator synthesized from L-arginine by endothelial cells. Inhibition of nitric oxide synthesis raises mean arterial pressure, lowers heart rate, and reverses the pregnancy-induced refractoriness to vasopressors. In humans, nitric oxide likely is the compound that maintains the normal low-pressure vasodilated state characteristic of fetoplacental perfusion (Myatt, 1992; Weiner, 1992). The effects of nitric oxide production in preeclampsia are unclear. It appears that the syndrome is associated with decreased endothelial nitric oxide synthase expression, thus resulting in lower nitric oxide activity (Davidge, 2015).

Endothelins are 21-amino-acid peptides and potent vasoconstrictors. Endothelin-1 (ET-1) is the primary isoform produced by human endothelium (Karumanchi, 2016b). Plasma ET-1 levels are elevated in normotensive pregnant women, but women with preeclampsia have even higher levels (Ajne, 2003). According to Taylor and Roberts (1999), the placenta is not the source of increased ET-1 concentrations, and they likely arise from systemic endothelial activation. Interestingly, treatment of preeclamptic women with magnesium sulfate lowers ET-1 concentrations (Sagsoz, 2003). And, in animal studies, sildenafil reduces ET-1 concentrations (Gillis, 2016).

Angiogenic and Antiangiogenic Proteins

Placental vasculogenesis is evident by 21 days after conception. The list of pro- and antiangiogenic substances involved in placental vascular development is extensive, and the families of vascular endothelial growth factor (VEGF) and angiopoietin are the most studied. *Angiogenic imbalance* describes excessive amounts of antiangiogenic factors, which are thought to be stimulated by worsening hypoxia at the uteroplacental interface. Trophoblast of women destined to develop preeclampsia overproduces at least two antiangiogenic peptides that enter the maternal circulation (Karumanchi, 2016a).

First, *soluble fms-like tyrosine kinase 1 (sFlt-1)* is a receptor for VEGF. As depicted in Figure 40-3, elevated maternal sFlt-1 levels inactivate and reduce circulating free placental growth factor (PlGF) and VEGF concentrations, leading to endothelial dysfunction (Maynard, 2003). Importantly, sFlt-1 levels begin to rise in maternal serum months before preeclampsia is evident (Fig. 40-4). These high levels in the second trimester are associated with a doubling of the risk for preeclampsia (Haggerty, 2012). This divergence from normal levels appears to develop even sooner with early-onset preeclampsia (Vatten, 2012). These factors are also operative in pregnancies complicated by fetal-growth restriction (Herraiz, 2012).

FIGURE 40-3

Schematic of the receptor blocking action of sFlt-1 (soluble fms-like tyrosine kinase 1) and soluble endoglin (sEng).

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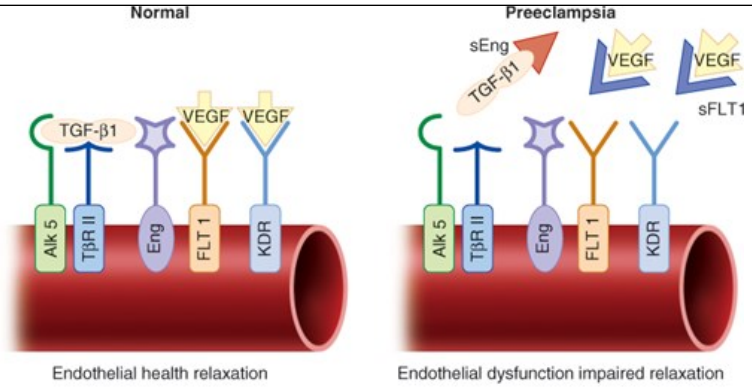

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FIGURE 40-4

Angiogenic and antiangiogenic factors in normotensive (NT) and preeclamptic (PE) women across pregnancy. Both pairs of factors are significantly divergent by 23 to 26 weeks' gestation. sFlt = soluble fms-like tyrosine kinase 1; PlGF = placental growth factor. (Data from Myatt, 2013.)

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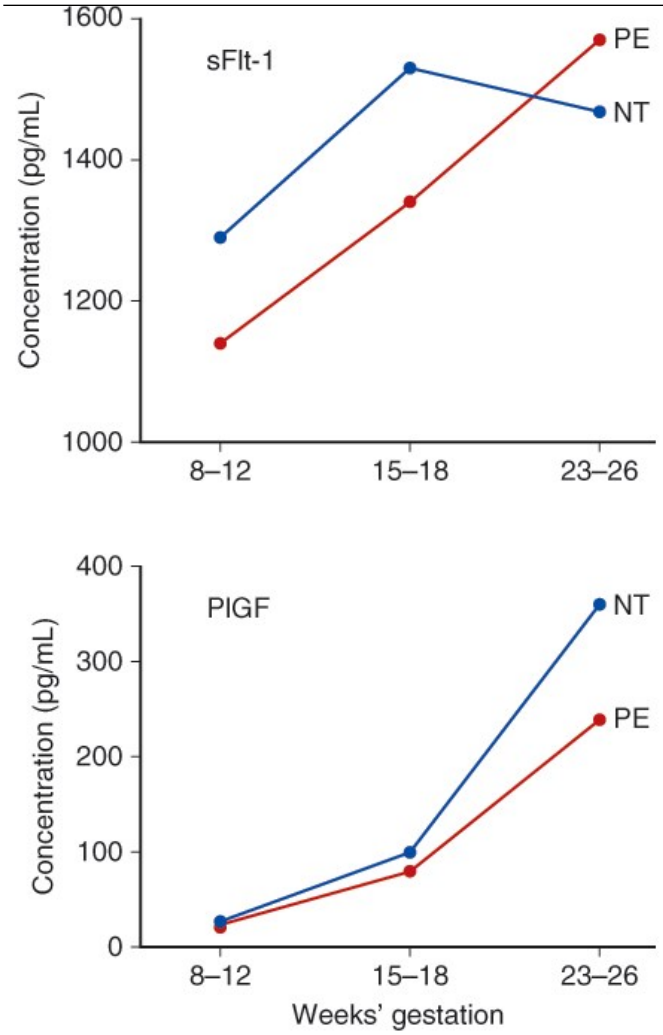

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A second antiangiogenic peptide, soluble endoglin (sEng), inhibits various transforming growth factor beta (TGF-β) isoforms from binding to endothelial receptors (see Fig. 40-3). Endoglin is one of these receptors. Decreased binding to endoglin diminishes endothelial nitric oxide-dependent vasodilatation. Serum levels of sEng also begin to rise months before clinical preeclampsia develops (Haggerty, 2012). Interestingly, metformin reduces antiangiogenic secretion from human tissues (Brownfoot, 2016).

In one systematic review, third-trimester elevation of sFlt-1 levels and lower PlGF concentrations correlate with preeclampsia development after 25 weeks' gestation (Widmer, 2007). Subsequently, Haggerty and coworkers (2012) reported that doubling of expressions of sFlt-1 and sEng increased the preeclampsia risk by 39 and 74 percent, respectively. The cause of placental overproduction of antiangiogenic proteins remains an enigma. There is a racial-ethnic difference in their secretion (Yang, 2016). Concentrations of the soluble forms are not higher in fetal circulation or amnionic fluid of preeclamptic women, and their levels in maternal blood dissipate after delivery (Staff, 2007).

Clinical research aims to employ antiangiogenic proteins in the prediction and diagnosis of preeclampsia. One preliminary report described therapeutic apheresis to reduce sFlt-1 levels (Thadhani, 2016).

PATHOPHYSIOLOGY

Evidence for preeclampsia manifestation begins early in pregnancy with covert pathophysiological changes that gain momentum across gestation and eventually become clinically apparent. Unless delivery supervenes, these changes ultimately lead to multiorgan involvement with a clinical spectrum ranging from meager findings to one of cataclysmic deterioration. As discussed, these are thought to be a consequence of endothelial dysfunction,

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vasospasm, and ischemia. Although the many maternal consequences of the preeclampsia syndrome are usually described in terms of individual organ systems, they frequently are multiple and overlap.

Cardiovascular System

Cardiovascular disturbances are common with preeclampsia syndrome. These are related to: (1) greater cardiac afterload caused by hypertension; (2) cardiac preload, which is reduced by a pathologically diminished volume expansion during pregnancy and which is increased by intravenous crystalloid or oncotic solutions; and (3) endothelial activation leading to interendothelial extravasation of intravascular fluid into the extracellular space and, importantly, into the lungs.

Hemodynamic Changes and Cardiac Function

The cardiovascular aberrations of pregnancy-related hypertensive disorders vary depending on several modifiers. These factors include preeclampsia severity, hypertension severity, presence of underlying chronic disease, and the part of the clinical spectrum in which these are studied. In some women, these cardiovascular changes may precede hypertension (De Paco, 2008; Easterling, 1990; Khalil, 2012; Melchiorre, 2013). Nevertheless, with the clinical onset of preeclampsia, cardiac output declines, due at least in part to greater peripheral resistance. When assessing cardiac function in preeclampsia, consideration is given to echocardiographic measures of *myocardial function* and to clinically relevant *ventricular function*.

Myocardial Function

Of women with preeclampsia, serial echocardiographic studies document diastolic dysfunction in 40 to 45 percent (Guirguis, 2015; Melchiorre, 2012). With this dysfunction, ventricles do not properly relax and cannot fill properly. In some of these women, functional differences persist up to 4 years after delivery (Evans, 2011; Orabona, 2017). Diastolic dysfunction stems from ventricular remodeling, which is judged to be an adaptive response to maintain normal contractility despite the increased afterload of preeclampsia. High levels of antiangiogenic proteins may be contributory (Shahul, 2016). In the otherwise healthy pregnant woman, these changes are usually clinically inconsequential. But when combined with underlying ventricular dysfunction—for example, concentric ventricular hypertrophy from chronic hypertension—further diastolic dysfunction may cause cardiogenic pulmonary edema (Wardhana, 2017). This is discussed further in Chapters 47 (Acute Respiratory Distress Syndrome) and 49 (Heart Failure).

Ventricular Function

Despite the relatively high frequency of diastolic dysfunction with preeclampsia, clinical cardiac function in most affected women is appropriate (Hibbard, 2015). In some preeclamptic women, cardiac troponin levels are slightly elevated, and amino-terminal pro-brain natriuretic peptide (Nt pro-BNP) levels are elevated with severe preeclampsia (Pergialiotis, 2016; Zachary, 2017). Importantly, both normally pregnant women and those with preeclampsia syndrome can have normal or slightly hyperdynamic ventricular function (Fig. 40-5). Thus, both have a cardiac output that is appropriate for left-sided filling pressures. Filling pressures are dependent on the volume of intravenous fluids. Thus, aggressive hydration results in overtly *hyperdynamic* ventricular function. This is accompanied by elevated pulmonary capillary wedge pressures, and pulmonary edema may develop despite normal ventricular function. This is because of an alveolar endothelial-epithelial leak, and it is compounded by decreased oncotic pressure from a low serum albumin concentration. In sum, aggressive fluid administration to otherwise normal women with severe preeclampsia substantially elevates normal left-sided filling pressures and raises a physiologically normal cardiac output to hyperdynamic levels.

FIGURE 40-5

Ventricular function in normally pregnant women (*striped area*) and in women with eclampsia (*boxed area*) is plotted on a Braunwald ventricular function curve. Normal values are from Clark (1989), and those for eclampsia are from Hankins (1984). PCWP = pulmonary capillary wedge pressure; LVSWI = left ventricular stroke work index.

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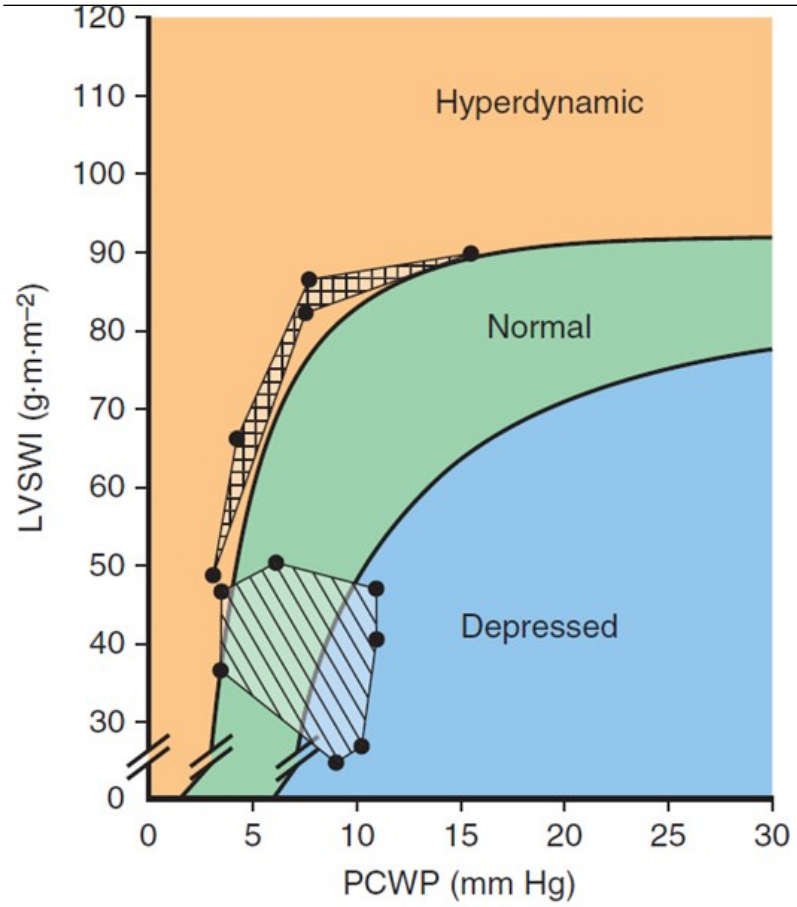

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Blood Volume

Hemoconcentration is a hallmark of eclampsia. This concept was precisely quantified by Zeeman and colleagues (2009), who expanded the prior observations of Pritchard and associates (1984). They showed in *eclamptic* women that the normally expected pregnancy blood volume expansion is severely curtailed (Fig. 40-6). Women of average size have a blood volume of 3000 mL, and during the last several weeks of a normal pregnancy, this averages 4500 mL. With *eclampsia*, however, much or all of the anticipated 1500 mL excess is lost. Such hemoconcentration results from generalized vasospasm that follows endothelial activation and leakage of plasma into the interstitial space. In women with *preeclampsia*, and depending on its severity, hemoconcentration is usually not as marked.

FIGURE 40-6

Total blood volumes in normotensive women compared with those with eclampsia. The vertical extensions are one standard deviation from the mean. In eclamptic women, blood volume is minimally increased compared with a subsequent normotensive pregnancy. (Data from Zeeman, 2009.)

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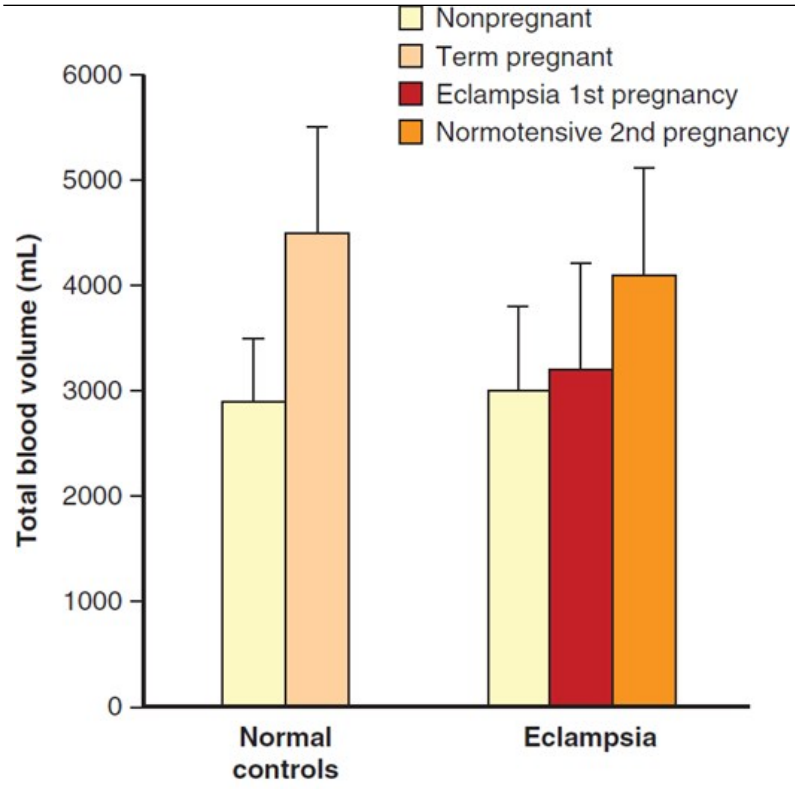

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These changes have substantial clinical consequences. Importantly, women with severe hemoconcentration are unduly sensitive to blood loss at delivery that otherwise may be considered normal. Vasospasm and endothelial leakage of plasma persist for a variable time after delivery as the endothelium is restored to normalcy. As this takes place, vasoconstriction reverses, and as the blood volume reexpands, the hematocrit usually falls. *Importantly, a substantive cause of this fall in hematocrit, however, is usually the blood loss incurred at delivery.* Anemia may also partially result from greater erythrocyte destruction as subsequently described.

Maternal Thrombocytopenia

The platelet count is routinely measured in women with any form of gestational hypertension. Decreased platelet concentrations with eclampsia were described more than 100 years ago. The frequency and intensity of thrombocytopenia vary and are dependent on the severity and duration of the preeclampsia syndrome (Heilmann, 2007; Hupuczi, 2007). Overt thrombocytopenia—defined by a platelet count <100,000/μL—indicates severe disease (see Table 40-2). In general, the lower the platelet count, the higher the rates of maternal and fetal morbidity and mortality (Leduc, 1992). In most cases, delivery is advisable because worsening thrombocytopenia usually ensues. After delivery, the platelet count may continue to decline for the first day or so. It then usually rises progressively to reach a normal level within 3 to 5 days. As discussed later (Brain), in some instances with HELLP syndrome, the platelet count continues to fall after delivery. If these do not reach a nadir until 48 to 72 hours, then preeclampsia syndrome may be incorrectly attributed to one of the thrombotic microangiopathies discussed in Chapter 56 (Thrombotic Microangiopathies).

Myriad other platelet alterations are attributed to the preeclampsia syndrome. These were reviewed by Kenny and coworkers (2015) and include platelet activation with increased α-degranulation producing β-thromboglobulin, factor 4, and enhanced clearance. Paradoxically, in most studies, in vitro platelet aggregation is reduced compared with the normal increase that is characteristic of pregnancy. This likely is due to platelet "exhaustion" following in vivo activation. Although the cause is unknown, immunological processes or simply platelet deposition at sites of endothelial damage may be implicated. Levels of platelet-bound and circulating platelet-bindable immunoglobulins are elevated, which suggests platelet surface alterations.

Abnormally low platelets do not develop in the fetuses or neonates born to preeclamptic women despite severe maternal thrombocytopenia (Kenny, 2015; Pritchard, 1987). *Thus, maternal thrombocytopenia in a hypertensive woman is not a fetal indication for cesarean delivery.*

Hemolysis

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Severe preeclampsia is frequently accompanied by hemolysis, which manifests as elevated serum lactate dehydrogenase levels and reduced haptoglobin levels. Other evidence comes from schizocytosis, spherocytosis, and reticulocytosis in peripheral blood (Cunningham, 1985; Pritchard, 1954, 1976). These derangements result in part from *microangiopathic hemolysis* caused by endothelial disruption with platelet adherence and fibrin deposition. Cunningham and coworkers (1995) postulated that erythrocyte morphology was partially caused by serum lipid alterations. Related, substantively decreased long-chain fatty acid content is found in erythrocytes of preeclamptic women (Mackay, 2012).

After early reports of hemolysis and thrombocytopenia with severe preeclampsia, descriptions were added of abnormally elevated serum liver transaminase levels that indicated hepatocellular necrosis (Chesley, 1978). Weinstein (1982) referred to this combination of events as the *HELLP syndrome*—and this term now is used worldwide. Also, facets of the HELLP syndrome are included in criteria that differentiate severe from nonsevere preeclampsia (see Table 40-2). The HELLP syndrome is discussed further in that section (Brain).

Coagulation Changes

Subtle changes consistent with intravascular coagulation, and less often erythrocyte destruction, commonly are found with preeclampsia and especially eclampsia (Cunningham, 2015; Kenny, 2015). Some of these changes include elevated factor VIII consumption, increased levels of fibrinopeptides A and B and of d-dimers, and reduced levels of regulatory proteins—antithrombin III and proteins C and S. Coagulation aberrations generally are mild and are seldom clinically significant (Kenny, 2015; Pritchard, 1984). Unless placental abruption is comorbid, plasma fibrinogen levels do not differ remarkably from levels found in normal pregnancy. Fibrin degradation products such as d-dimers are minimally elevated. As preeclampsia worsens, so do abnormal findings with *thromboelastography* (Pisani-Conway, 2013). Despite these changes, routine laboratory assessments of coagulation, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and plasma fibrinogen level, are not required in the management of pregnancy-associated hypertensive disorders.

Endocrine and Hormonal Alterations

Plasma levels of *renin, angiotensin II*, *angiotensin 1–7, aldosterone, deoxycorticosterone,* and *atrial natriuretic peptide (ANP)* are substantively augmented during normal pregnancy. ANP is released during atrial wall stretching from blood volume expansion, and it responds to cardiac contractility (Chap. 4, Renin, Angiotensin II, and Plasma Volume). Levels of serum ANP rise in pregnancy, and its secretion is further enhanced in women with preeclampsia (Luft, 2009). Levels of its precursor—*proatrial natriuretic peptide*—are also increased in preeclampsia (Sugulle, 2012). *Vasopressin* levels are similar in nonpregnant, normally pregnant, and preeclamptic women even though the metabolic clearance is elevated in the latter two (Dürr, 1999).

Fluid and Electrolyte Alterations

In women with severe preeclampsia, the volume of *extracellular fluid,* manifest as edema, is usually much greater than that in normal pregnant women. As discussed, the mechanism responsible for pathological fluid retention is endothelial injury (Davidge, 2015). In addition to generalized edema and proteinuria, these women have reduced plasma oncotic pressure. This reduction creates a filtration imbalance and further displaces intravascular fluid into the surrounding interstitium. Electrolyte concentrations do not differ appreciably in women with preeclampsia compared with those of normal pregnant women.

Following an eclamptic convulsion, the *serum pH* and *bicarbonate* concentration are lowered due to lactic acidosis and compensatory respiratory loss of carbon dioxide. The intensity of acidosis relates to the amount of lactic acid produced—metabolic acidosis—and the rate at which carbon dioxide is exhaled—respiratory acidosis.

Kidney

During normal pregnancy, renal blood flow and glomerular filtration rate rise appreciably (Chap. 4, Urinary System). With preeclampsia, several reversible anatomical and pathophysiological changes ensue. Of clinical importance, renal perfusion and glomerular filtration are reduced. Levels that are much less than normal nonpregnant values are infrequent and are the consequence of severe disease. Most of the decrement in glomerular filtration is from higher renal afferent arteriolar resistance that may be elevated up to fivefold (Conrad, 2015; Cornelis, 2011). Morphological changes are characterized by *glomerular endotheliosis*, which blocks the barrier that allows filtration. Diminished filtration causes serum creatinine levels to rise to values seen in nonpregnant individuals, that is, 1 mg/mL, and sometimes higher (Lindheimer, 2008a). Abnormal values usually begin to

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normalize 10 days or later after delivery (Cornelis, 2011; Spaan, 2012a).

In most preeclamptic women, the urine sodium concentration is elevated. Urine osmolality rises, urine:plasma creatinine ratio is elevated, and fractional excretion of sodium is low, which all indicated that a prerenal mechanism is involved. Sodium-containing crystalloid infusion raises left ventricular filling pressure, and although oliguria temporarily improves, rapid infusions may cause clinically apparent pulmonary edema. Intensive intravenous fluid therapy is not indicated as "treatment" for preeclamptic women with oliguria unless urine output is diminished from hemorrhage or fluid loss from vomiting or fever.

Plasma uric acid concentration is typically elevated in preeclampsia. The elevation exceeds that attributable to the reduction in glomerular filtration rate and likely is also due to enhanced tubular reabsorption (Chesley, 1945). At the same time, preeclampsia is associated with diminished urinary excretion of calcium, perhaps because of greater tubular reabsorption (Taufield, 1987).

Proteinuria

As shown in Table 40-1, detection of proteinuria helps to establish the diagnosis of preeclampsia. Abnormal protein excretion is empirically defined by 24-hour urinary excretion exceeding 300 mg; a urine protein:creatinine ratio ≥0.3; or persistent protein values of 30 mg/dL (1+ dipstick) in random urine samples. Although worsening or nephrotic-range proteinuria has been considered by most to be a sign of severe disease, this does not appear to be the case (Airoldi, 2007). Certainly, this concept was not accepted by the 2013 Task Force.

Problematically, the optimal method of establishing abnormal levels of either urine protein or albumin remains to be defined. For a 24-hour quantitative specimen, the "consensus" threshold value used is ≥300 mg/24 h (American College of Obstetricians and Gynecologists, 2013). Using a urinary protein excretion threshold of 165 mg in a 12-hour sample shows equivalent efficacy (Stout, 2015; Tun, 2012).

Determination of urinary protein:creatinine ratio may supplant the cumbersome 24-hour quantification (Kyle, 2008; Morris, 2012). Chen and associates (2008) found that clean-catch and catheterized urine specimens correlate well. In one systematic review, random urine protein:creatinine ratios below 130 to 150 mg/g, that is, 0.13 to 0.15, indicate a low likelihood of proteinuria exceeding 300 mg/d (Papanna, 2008). Ratios <0.08 or >1.19 have negative- or positive-predictive values of 86 and 96 percent, respectively (Stout, 2013). However, midrange ratios, that is, 300 mg/g or 0.3, have poor sensitivity and specificity. Thus, many recommend that with midrange ratio values, 24-hour protein excretion should be quantified.

With urine dipstick assessment, determinations depend on urine concentration and are notorious for false-positive and -negative results. Thus, assessment may show a dipstick value of 1+ to 2+ from concentrated urine specimens from women who excrete <300 mg/d.

Importantly, proteinuria may develop late, and some women may already be delivered or have had an eclamptic convulsion before it appears. For example, 10 to 15 percent of women with HELLP syndrome do not have proteinuria at presentation (Sibai, 2004). In one report, 17 percent of eclamptic women did not have proteinuria by the time of seizures (Zwart, 2008).

Anatomical Changes

Sheehan and Lynch (1973) frequently found changes identifiable at autopsy by light and electron microscopy in the kidneys of eclamptic women. Glomeruli are enlarged by approximately 20 percent, they are "bloodless," and capillary loops variably are dilated and contracted. Endothelial cells are swollen—termed *glomerular capillary endotheliosis* (Spargo, 1959). Endothelial cells are often so swollen that they block or partially block the capillary lumens (Fig. 40-7) (Hecht, 2017). Homogeneous subendothelial deposits of proteins and fibrin-like material are seen.

FIGURE 40-7

Schematic showing glomerular capillary endotheliosis. The capillary of the normal glomerulus shown on the left has wide endothelial fenestrations, and the pedicels emanating from the podocytes are widely spaced (*arrow*). The illustration on the right is of a glomerulus with changes induced by the preeclampsia syndrome. The endothelial cells are swollen and their fenestrae narrowed, as are the pedicels that now abut each other.

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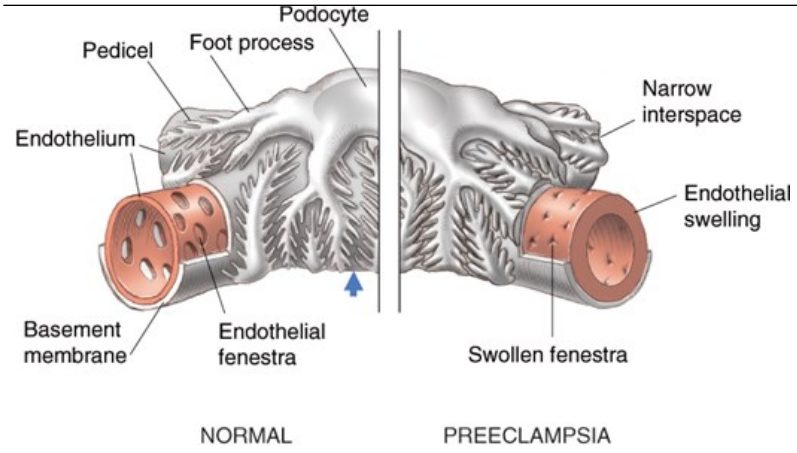

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Endothelial swelling may result from angiogenic protein "withdrawal" caused by the complexing of free angiogenic proteins with a compatible circulating antiangiogenic protein receptor (see Fig. 40-3). The angiogenic proteins are crucial for podocyte health, and their inactivation leads to podocyte dysfunction and endothelial swelling (Conrad, 2015; Karumanchi, 2009). Also, eclampsia is characterized by greater excretion of these epithelial podocytes (Wagner, 2012; White, 2014).

Acute Kidney Injury

Although mild degrees of acute kidney injury are encountered, clinically apparent *acute tubular necrosis* is almost invariably induced by comorbid hemorrhage with hypovolemia and hypotension (Chap. 41, General Considerations). This is usually caused by severe obstetrical bleeding—especially placental abruption—coupled with inadequate blood replacement. Drakeley and coworkers (2002) described 72 women with preeclampsia and renal failure. Half had HELLP syndrome, and a third had placental abruption. In one review of 183 women with HELLP syndrome, 5 percent had kidney injury (Haddad, 2000). Of those with renal injury, half had placental abruption, and most had postpartum hemorrhage. Last, irreversible *renal cortical necrosis* develops rarely (Chap. 53, Lower Genital Tract Lesions).

Liver

The characteristic hepatic lesions with eclampsia are regions of periportal hemorrhage in the liver periphery (Hecht, 2017). However, lesions as extensive as those shown in Figure 40-8 are unusual. Sheehan and Lynch (1973) described that some degree of hepatic infarction accompanied hemorrhage in almost half of women who died with eclampsia. These findings corresponded with reports during the 1960s that described elevated serum hepatic transaminase levels. Along with the earlier observations by Pritchard and associates (1954), who described hemolysis and thrombocytopenia with eclampsia, this constellation of hemolysis, hepatocellular necrosis, and thrombocytopenia was later termed *HELLP syndrome*.

FIGURE 40-8

Gross liver specimen from a woman with preeclampsia who died from aspiration pneumonitis. Periportal hemorrhagic necrosis was seen microscopically. (Reproduced with permission from Cunningham FG: Liver disease complicating pregnancy. Williams Obstetrics, 19th ed. (Suppl 1), Norwalk, Appleton & Lange, 1993.)

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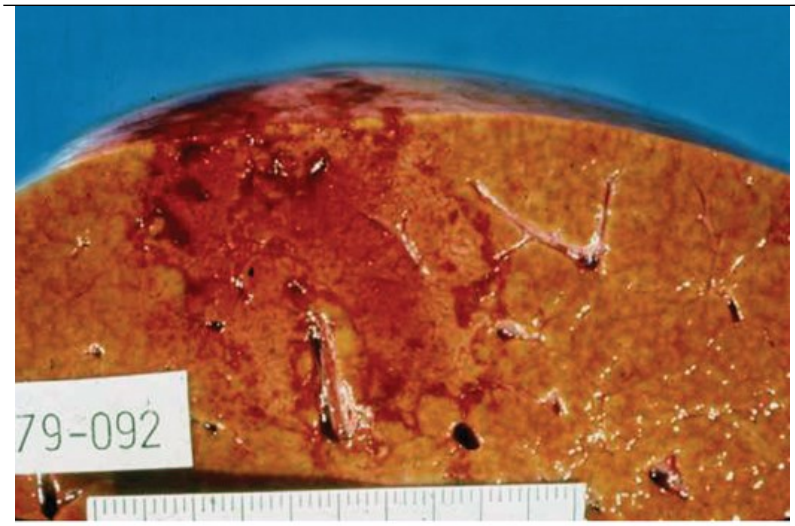

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Liver involvement with preeclampsia may clinically display at least three manifestations. First, pain is considered a sign of severe disease. It typically manifests by moderate-to-severe right upper quadrant or midepigastric pain and tenderness. Such women usually have elevated serum aspartate transaminase (AST) or alanine transaminase (ALT) levels. In some cases, however, the amount of hepatic tissue involved with infarction may be surprisingly extensive yet still clinically insignificant (Nelson, 2017). In our experiences, infarction may be worsened by hypotension from obstetrical hemorrhage, and it occasionally causes hepatic failure—also called shock liver (Alexander, 2009; Yoshihara, 2016).

Second, elevations of serum AST and ALT levels are markers for severe preeclampsia. Values seldom exceed 500 U/L, but levels reaching more than 2000 U/L have been reported (Chap. 55, Hepatic Disorders). In general, serum concentrations inversely follow platelet levels, and they both usually normalize within 3 days following delivery.

As a third presentation, hemorrhagic infarction may extend to form a hepatic hematoma. This in turn can extend to form a subcapsular hematoma that may rupture. Computed tomography (CT) scanning or magnetic resonance (MR) imaging greatly aids diagnosis (Fig. 40-9). Unruptured hematomas are probably more common than clinically suspected and are more likely to be found with HELLP syndrome. Although once considered a surgical condition, current management of a hepatic hematoma usually consists of observation unless bleeding is ongoing. In some cases, however, prompt surgical intervention or angiographic embolization may be lifesaving. In one review of 180 cases of hepatic hematoma or rupture, 94 percent of affected gravidas had HELLP syndrome, and in 90 percent of the total, the capsule had ruptured (Vigil-De Gracia, 2012). The maternal mortality rate was 22 percent, and the perinatal mortality rate was 31 percent. In rare cases, liver transplantation is necessary (Hunter, 1995; Wicke, 2004).

FIGURE 40-9

Abdominal CT imaging performed postpartum in a woman with severe HELLP syndrome and right-upper quadrant pain. A large subcapsular hematoma (*asterisk*) is seen confluent with intrahepatic infarction and hematoma (*arrowhead*). Numerous flame-shaped hemorrhages are seen at the hematoma interface (*arrows*).

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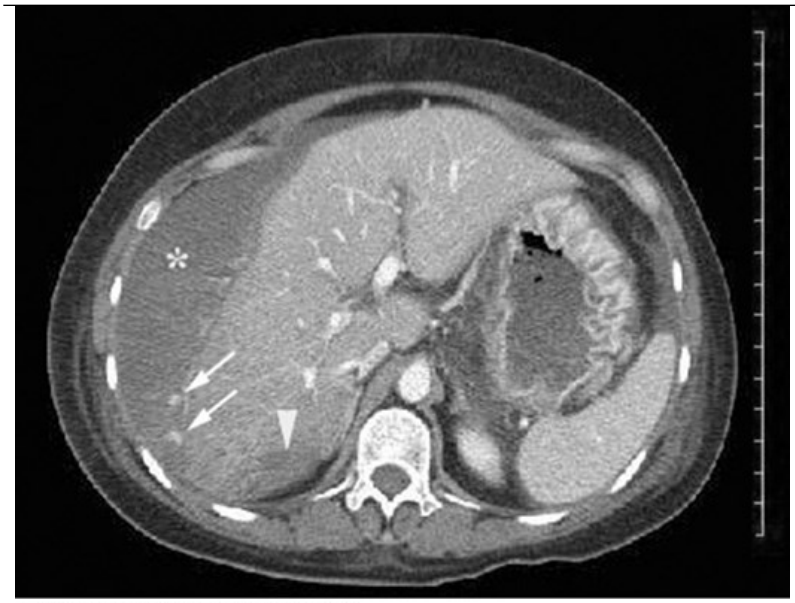

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Acute fatty liver of pregnancy is sometimes confused with preeclampsia (Nelson, 2013; Sibai, 2007a). It too has an onset in late pregnancy, and often there is accompanying hypertension, elevated serum transaminase and creatinine levels, and thrombocytopenia. However, the hallmark of acute fatty liver is significant liver dysfunction, and Table 55-1 highlights these clinical differences.

Last, no convincing data link pancreatic involvement with preeclampsia syndrome (Sheehan, 1973). Thus, the occasional case of concurrent hemorrhagic pancreatitis is likely unrelated (Lynch, 2015; Swank, 2012). In our experiences from Parkland Hospital, amylase levels were seldom elevated in preeclamptic women (Nelson, 2014a).

HELLP Syndrome

There is no universally accepted strict definition of HELLP syndrome, and thus its incidence varies by investigator. In the previously noted study of 183 women with HELLP syndrome, 40 percent had adverse outcomes, and two mothers died (Haddad, 2000). Complications included eclampsia in 6 percent, placental abruption—10 percent, acute kidney injury—5 percent, and pulmonary edema—10 percent. Stroke, hepatic hematoma, coagulopathy, acute respiratory distress syndrome, and sepsis were other serious complications.

Women with preeclampsia and HELLP syndrome typically have worse outcomes than preeclamptic women without the HELLP constellation (Kozic, 2011; Martin, 2012, 2013). In one review of 693 women with HELLP syndrome, 10 percent had concurrent eclampsia (Keiser, 2011). Sep and associates (2009) described a significantly higher risk for complications in women with HELLP syndrome compared with those with "isolated preeclampsia." These included eclampsia—15 versus 4 percent; preterm birth—93 versus 78 percent; and perinatal mortality rate—9 versus 4 percent, respectively. Because of these marked clinical differences, it has been postulated that HELLP syndrome has a distinct pathogenesis (Reimer, 2013; Vaught, 2016).

Brain

Headaches and visual symptoms are common with severe preeclampsia, and associated convulsions define eclampsia. The earliest anatomical descriptions of brain involvement came from autopsy specimens, but CT and MR imaging and Doppler studies have added many important insights.

Neuroanatomical Lesions

From early anatomical descriptions, brain pathology accounted for only about a third of fatal cases such as the one shown in Figure 40-10. In fact, most deaths were from pulmonary edema, and brain lesions were coincidental. Thus, although gross intracerebral hemorrhage was seen in up to 60 percent of eclamptic women, it was fatal in only half of these (Melrose, 1984; Richards, 1988; Sheehan, 1973). As shown in Figure 40-11, other principal lesions found at autopsy of eclamptic women were cortical and subcortical petechial hemorrhages. The classic microscopic vascular lesions consist of fibrinoid necrosis of the arterial wall and perivascular microinfarcts and hemorrhages. Other frequently described major lesions include subcortical

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edema, multiple nonhemorrhagic areas of "softening" throughout the brain, and hemorrhagic areas in the white matter (Hecht, 2017). There also may be hemorrhage in the basal ganglia or pons, sometimes with rupture into the ventricles.

FIGURE 40-10

This autopsy brain slice shows a fatal hypertensive hemorrhage in a primigravida with eclampsia.

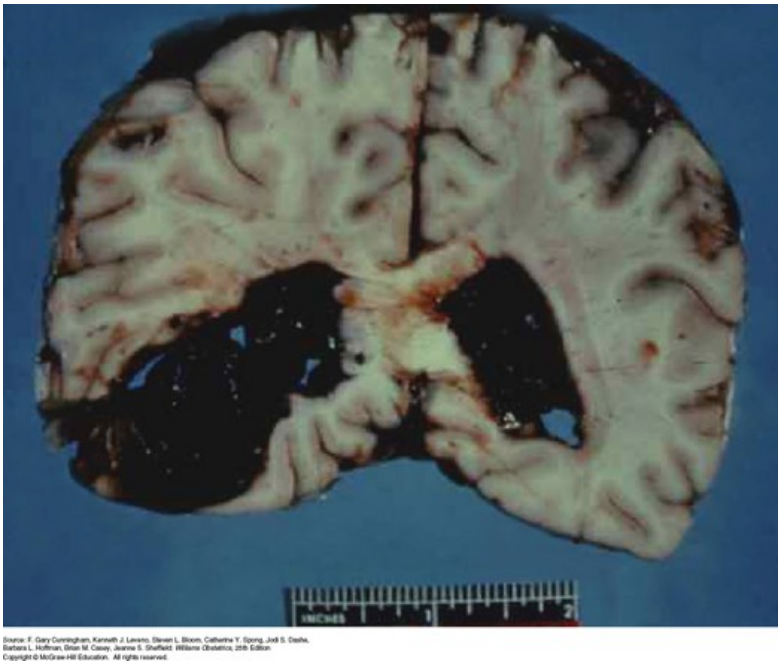

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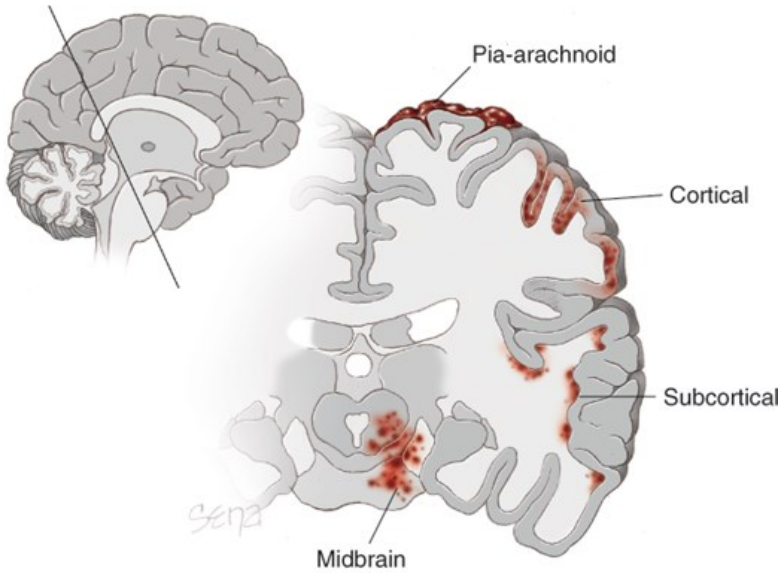
FIGURE 40-11

Composite illustration showing location of cerebral hemorrhages and petechiae in women with eclampsia. Insert shows the level of the brain from which the main image was constructed. (Data from Sheehan, 1973.)



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Cerebrovascular Pathophysiology

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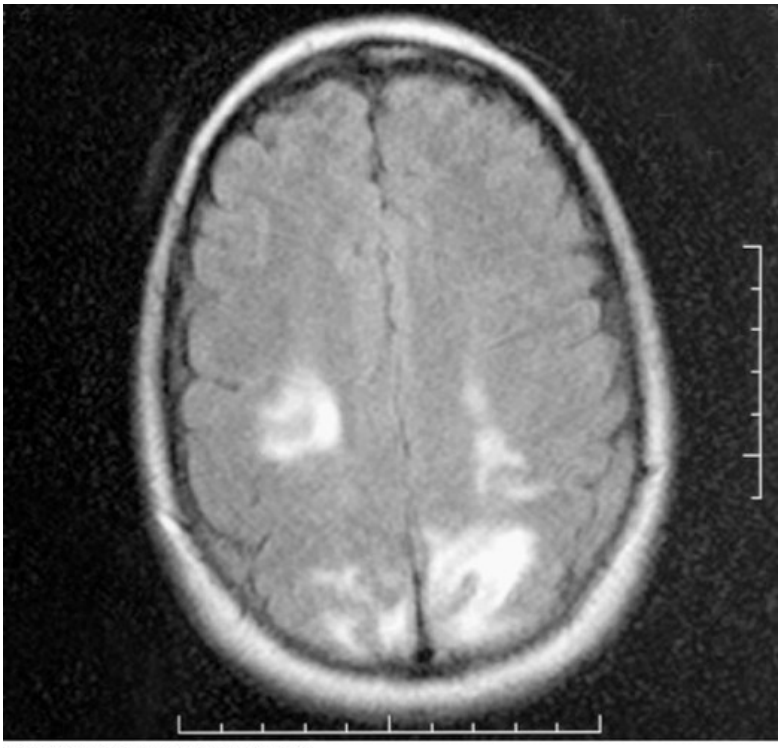
Clinical, pathological, and neuroimaging findings have led to two general theories to explain cerebral abnormalities with eclampsia. Importantly, endothelial cell dysfunction that characterizes the preeclampsia syndrome likely is a key in both. The first theory suggests that in response to acute and severe hypertension, cerebrovascular overregulation leads to vasospasm (Trommer, 1988). In this scheme, diminished cerebral blood flow is hypothesized to result in ischemia, cytotoxic edema, and eventually tissue infarction. Little objective evidence supports this mechanism.

The second theory is that sudden elevations in systemic blood pressure exceed the normal cerebrovascular autoregulatory capacity (Hauser, 1988; Schwartz, 2000). Regions of forced vasodilation and vasoconstriction develop, especially in arterial boundary zones. At the capillary level, disruption of end-capillary pressure causes increased hydrostatic pressure, hyperperfusion, and extravasation of plasma and red cells through endothelial tight-junction openings. This leads to *vasogenic edema*. The recent description of a central nervous system lymphatic vasculature lends credibility to this theory (Louveau, 2015).

The most likely mechanism is a combination of the two. Thus, a preeclampsia-associated interendothelial cell leak develops at blood pressure (hydraulic) levels much lower than those that usually cause vasogenic edema and is coupled with a loss of upper-limit autoregulation (Fugate, 2015; Zeeman, 2009). With imaging studies, these manifest as the *posterior reversible encephalopathy syndrome* (Fig. 40-12) (Fugate, 2015; Hinchey, 1996). The lesions of this syndrome principally involve the posterior brain—the occipital and parietal cortices. But, in at least a third of cases, other areas are involved (Edlow, 2013; Zeeman, 2004a).

FIGURE 40-12

Cranial magnetic-resonance imaging in a nullipara with eclampsia. Multilobe T2-FLAIR high-signal lesions are apparent. FLAIR = fluid-attenuated inversion recovery. (Used with permission from Dr. Gerda Zeeman.)



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Cerebral Blood Flow

Autoregulation is the mechanism by which cerebral blood flow remains relatively constant despite alterations in cerebral perfusion pressure. Remember that cerebral perfusion pressure is the difference between mean arterial pressure and intracranial pressure. In nonpregnant individuals, this autoregulation protects the brain from hyperperfusion when mean arterial pressures rise to as high as 160 mm Hg. These are pressures far greater than those seen in all but a very few women with eclampsia. Thus, to explain eclamptic seizures, it was theorized that autoregulation must be altered by

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pregnancy. Studies by Cipolla and colleagues (2007, 2009, 2015) have convincingly shown that autoregulation is unchanged across pregnancy in rodents. But, some investigators have provided evidence of impaired autoregulation in women with preeclampsia (Janzarik, 2014; van Veen, 2013).

Zeeman and associates (2003) showed that cerebral blood flow during the first two trimesters of normal pregnancy is similar to nonpregnant values. But during the last trimester, flow significantly drops by 20 percent. This group also found greater cerebral blood flow in this trimester in women with severe preeclampsia compared with that in normotensive pregnant women (Zeeman, 2004b). Taken together, these findings suggest that eclampsia occurs when cerebral hyperperfusion forces capillary fluid interstitially because of endothelial damage. This leak leads to perivascular edema characteristic of the preeclampsia syndrome.

Neurological Manifestations

Several neurological manifestations typify the preeclampsia syndrome. Each signifies severe involvement and requires immediate attention.

First, *headache and scotomata* are thought to arise from cerebrovascular hyperperfusion that has a predilection for the occipital lobes. Up to 75 percent of women have headaches, and 20 to 30 percent have visual changes preceding eclamptic convulsions (Sibai, 2005; Zwart, 2008). The headaches may be mild to severe and intermittent to constant. In our experiences, they are unique in that they do not usually respond to traditional analgesia, but they frequently improve after magnesium sulfate infusion.

Convulsions are diagnostic for eclampsia. These are caused by excessive release of excitatory neurotransmitters—especially glutamate; massive depolarization of network neurons; and bursts of action potentials (Meldrum, 2002). Clinical and experimental evidence suggests that extended seizures can cause significant brain injury and later brain dysfunction.

Blindness is rare with preeclampsia alone, but it complicates eclamptic convulsions in up to 15 percent of women (Cunningham, 1995). Blindness may develop up to a week or more following delivery (Chambers, 2004). There are at least two types of blindness, as discussed subsequently.

Generalized cerebral edema may develop and is usually manifest by mental status changes that vary from confusion to coma. This situation is particularly dangerous because fatal transtentorial herniation can result.

Last, women with eclampsia have been shown to have some cognitive decline when studied 5 to 10 years following an eclamptic pregnancy. This is discussed further in the final section (Renal Sequelae).

Neuroimaging Studies

With CT imaging, localized hypodense lesions at the gray- and white-matter junction, primarily in the parietooccipital lobes, are typically found in eclampsia. Such lesions may also be seen in the frontal and inferior temporal lobes, the basal ganglia, and thalamus (Brown, 1988). These hypodense areas correspond to petechial hemorrhages and local edema. Edema of the occipital lobes or diffuse cerebral edema may cause symptoms such as blindness, lethargy, and confusion (Cunningham, 2000). Widespread edema can appear as marked compression or even obliteration of the cerebral ventricles. Such women may develop signs of impending life-threatening transtentorial herniation.

Several MR imaging acquisitions are used to study eclamptic women. Common findings are hyperintense T2 lesions—namely, posterior reversible encephalopathy syndrome (PRES)—in the subcortical and cortical regions of the parietal and occipital lobes (see Fig. 40-12). Also, the basal ganglia, brainstem, and cerebellum are relatively commonly involved (Brewer, 2013; Zeeman, 2004a). Again, these lesions represent focal cerebral edema. Although these PRES lesions are almost universal in women with eclampsia, their incidence in women with preeclampsia approximates 20 percent (Mayama, 2016). Lesions are more likely in women who have severe disease and who have neurological symptoms. And although usually reversible, a fourth of these hyperintense lesions represent cerebral infarctions that have persistent findings (Loureiro, 2003; Zeeman, 2004a).

Visual Changes and Blindness

Scotomata, blurred vision, or diplopia are common with severe preeclampsia and eclampsia. These usually improve with magnesium sulfate therapy and/or lowered blood pressure. Blindness is less common, is usually reversible, and may arise from three potential areas. These are the visual cortex of the occipital lobe, the lateral geniculate nuclei, and the retina. In the retina, pathological lesions may be ischemia, infarction, or detachment (Handor, 2014; Roos, 2012).

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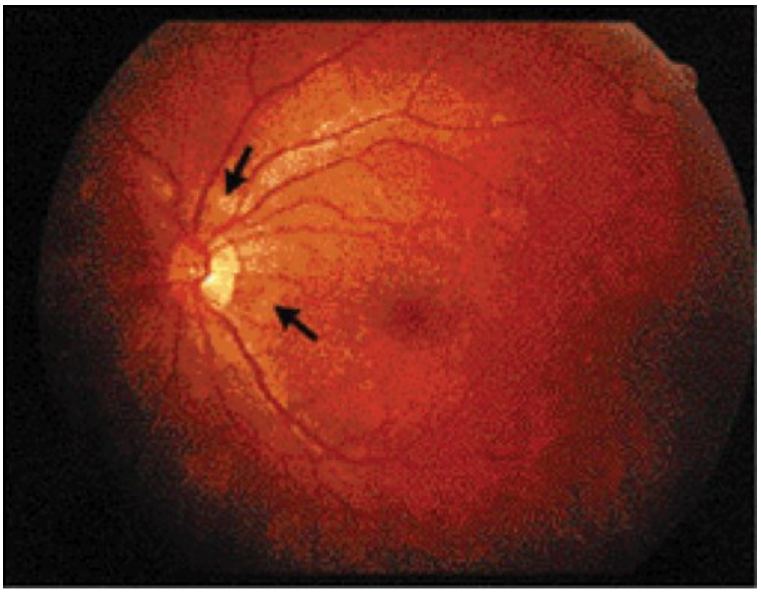
Occipital blindness is also called *amaurosis*—from the Greek *dimming*. With imaging, affected women usually have evidence of extensive occipital lobe vasogenic edema. Of 15 women cared for at Parkland Hospital, occipital blindness lasted from 4 hours to 8 days, but it resolved completely in all cases (Cunningham, 1995). Rarely, extensive cerebral infarctions may result in total or partial visual defects.

Blindness from retinal lesions is caused either by serous retinal detachment or rarely by retinal infarction, which is termed *Purtscher retinopathy* (Fig. 40-13). *Serous retinal detachment* is usually unilateral and seldom causes total visual loss. In fact, asymptomatic serous retinal detachment is relatively common with preeclampsia (Saito, 1998). In most cases of eclampsia-associated blindness, visual acuity subsequently improves. However, if blindness is caused by retinal artery occlusion, vision may be permanently impaired (Lara-Torre, 2002; Moseman, 2002; Roos, 2012).

FIGURE 40-13

Purtscher retinopathy caused by choroidal ischemia and infarction in preeclampsia syndrome. Ophthalmoscopy shows scattered yellowish, opaque lesions of the retina (*arrows*). (Reproduced with permission from Lam DS, Chan W: Images in clinical medicine. Choroidal ischemia in preeclampsia. N Engl J Med 344(10):739, 2001.)



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Cerebral Edema

Clinical manifestations suggesting widespread cerebral edema are worrisome. During 13 years at Parkland Hospital, 10 of 175 women (6 percent) with eclampsia were diagnosed with symptomatic cerebral edema (Cunningham, 2000). Symptoms ranged from lethargy, confusion, and blurred vision to obtundation and coma. In most cases, symptoms waxed and waned. Mental status changes generally correlated with the degree of involvement seen with CT and MR imaging studies. *These women are very susceptible to sudden and severe blood pressure elevations, which can acutely worsen the already widespread vasogenic edema.* Thus, careful blood pressure control is essential. In the 10 women with generalized edema, three became comatose and had imaging findings of transtentorial herniation, from which one died. Consideration is given for treatment with mannitol or dexamethasone.

Uteroplacental Perfusion

Compromised uteroplacental perfusion is almost certainly a major culprit in the greater perinatal morbidity and mortality rates seen with preeclampsia (Harmon, 2015). Defects in endovascular trophoblastic invasion with the preeclampsia syndrome were discussed earlier (Etiology). Thus, measurement of uterine, intervillous, and placental blood flow would likely be informative. Attempts to assess these in humans have been hampered by several obstacles that include inaccessibility of the placenta, the complexity of its venous effluent, and the need for radioisotopes or invasive techniques.

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Measurement of uterine artery blood flow velocity has been used to estimate resistance to uteroplacental blood flow (Chap. 17, Amnionic Fluid Volume). Vascular resistance is estimated by comparing arterial systolic and diastolic velocity waveforms. By the completion of placentation, impedance of uterine artery blood flow is markedly decreased, but with abnormal placentation, abnormally high resistance persists (Everett, 2012; Ghidini, 2008; Napolitano, 2012). Earlier studies were done to assess this by measuring peak systolic:diastolic velocity ratios from uterine and umbilical arteries in preeclamptic pregnancies. In some cases, but certainly not all, there was higher resistance (Fleischer, 1986; Trudinger, 1990).

Another Doppler waveform—uterine artery "notching"—has been associated with elevated risks for preeclampsia or fetal-growth restriction (Groom, 2009). In the MFMU Network study reported by Myatt and colleagues (2012a), however, notching had a low predictive value except for early-onset severe disease.

Resistance in *uterine spiral arteries* has also been measured. Impedance was higher in peripheral than in central vessels—a "ring-like" distribution (Matijevic, 1999). Mean resistance values were greater in all women with preeclampsia compared with those in normotensive controls. One study used MR imaging and other techniques to assess placental perfusion ex vivo in myometrial arteries removed from women with preeclampsia or fetal-growth restriction (Ong, 2003). In both conditions, myometrial arteries exhibited endothelium-dependent vasodilatory response. Moreover, other pregnancy conditions are also associated with increased resistance (Urban, 2007). One major adverse effect, fetal-growth restriction, is discussed in Chapter 44 (Fetal-Growth Restriction).

de Almeida Pimenta and colleagues (2014) assessed placental vascularity using a three-dimensional power Doppler histogram and described a *placental vascularity index*. This index value was reduced in women with any pregnancy-associated hypertensive disorders—11.1 percent compared with 15.2 percent in normal controls.

Despite these findings, evidence for compromised uteroplacental circulation is found in only a few women who go on to develop preeclampsia. Indeed, when preeclampsia develops during the third trimester, only a third of women with severe disease have abnormal uterine artery velocimetry (Li, 2005). In a study of 50 women with HELLP syndrome, only a third had abnormal uterine artery waveforms (Bush, 2001). In general, the extent of abnormal waveforms correlates with severity of fetal involvement (Ghidini, 2008; Groom, 2009).

PREDICTION

Various biological markers implicated in the preeclampsia syndrome have been measured to help predict its development. Although most have been evaluated in the first half of pregnancy, some have been tested as predictors of severity in the third trimester (Chaiworapongsa, 2013; Lai, 2013; Mosimann, 2013). Others have been used to forecast recurrent preeclampsia (Demers, 2014; Eichelberger, 2015). Some of these tests are listed in Table 40-5, which is by no means all inclusive.

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TABLE 40-5

Predictive Tests for Development of the Preeclampsia Syndrome

Testing Related To:	Examples
Placental perfusion/vascular resistance	Roll-over test, isometric handgrip or cold pressor test, pressor response to aerobic exercise, angiotensin-II infusion, midtrimester mean arterial pressure, platelet angiotensin-II binding, renin, 24-hour ambulatory blood pressure monitoring, uterine artery or fetal transcranial Doppler velocimetry
Fetal-placental unit endocrine dysfunction	Human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), estriol, pregnancy-associated protein A (PAPP A), inhibin A, activin A, placental protein 13, procalcitonin, corticotropin-releasing hormone, A disintegrin, ADAM-12, kisspeptin
Renal dysfunction	Serum uric acid, microalbuminuria, urinary calcium or kallikrein, microtransferrinuria, *N*-acetyl-β-glucosaminidase, cystatin C, podocyturia, podocalyxin
Endothelial dysfunction/oxidant stress	Platelet count and activation, fibronectin, endothelial adhesion molecules, prostaglandins, prostacyclin, MMP-9, thromboxane, C-reactive protein, cytokines, endothelin, neurokinin B, homocysteine, lipids, insulin resistance, resistin, antiphospholipid antibodies, plasminogen activator-inhibitor (PAI), leptin, p-selectin, angiogenic and antiangiogenic factors such as placental growth factor (PlGF), vascular endothelial growth factor (VEGF), fms-like tyrosine kinase receptor-1 (sFlt-1), endoglin
Others	Antithrombin-III(AT-3), atrial natriuretic peptide (ANP), β_2-microglobulin, haptoglobin, transferrin, ferritin, 25-hydroxyvitamin D, genetic markers, cell-free fetal DNA, serum and urine proteomics and metabolomic markers, hepatic aminotransferases

ADAM12 = ADAM metallopeptidase domain 12; MMP = matrix metalloproteinase.

Adapted from Conde-Agudelo, 2015, Duckworth, 2016.

Overall, these efforts have resulted in testing strategies with poor sensitivity and with poor positive-predictive values for preeclampsia (Conde-Agudelo, 2015; Odibo, 2013). *Currently, no screening tests for preeclampsia are predictably reliable, valid, and economical.* However, combinations of tests, some yet to be adequately evaluated, may be promising (Gallo, 2016; Olsen, 2012).

Vascular Resistance Testing and Placental Perfusion

Most tests in this category are cumbersome, time consuming, and overall inaccurate. To evaluate blood pressure changes, three tests assess the blood pressure rise in response to a stimulus. In one, women at 28 to 32 weeks' gestation rest in the left lateral decubitus position and then roll to the supine position. With this *roll-over test,* increased blood pressure with this maneuver signifies a positive test. The *isometric exercise test* employs the same principle by squeezing a handball. The *angiotensin II infusion test* is performed by giving incrementally increasing doses intravenously, and the hypertensive response is quantified. In an updated metaanalysis, sensitivities of all three tests were reported to range from 55 to 70 percent, and specificities approximated 85 percent (Conde-Agudelo, 2015).

Uterine artery Doppler velocimetry is posited to reflect faulty trophoblastic invasion of the spiral arteries. This failure results in diminished placental perfusion and upstream greater uterine artery resistance. Increased uterine artery velocimetry determined by Doppler ultrasound in the first two trimesters might provide indirect evidence of this process and thus serve as a predictive test for preeclampsia (Dar, 2010; Groom, 2009). Elevated flow resistance results in an abnormal vessel waveform represented by an exaggerated *diastolic notch.* These findings have value for prediction of fetal-growth restriction but not preeclampsia (American College of Obstetricians and Gynecologists, 2015). Several flow velocity waveforms have been investigated for preeclampsia prediction, however, none is suitable for clinical use (Conde-Agudelo, 2015; Kleinrouweler, 2012; Myatt, 2012a).

Fetal-Placental Unit Endocrine Function

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Several serum analytes have been proposed to help predict preeclampsia (see Table 40-5). Newer ones are continually added. In general, none of these tests are clinically beneficial for hypertension prediction.

Renal Function Tests

Hyperuricemia likely results from reduced uric acid clearance from diminished glomerular filtration, increased tubular reabsorption, and decreased secretion. Cnossen and coworkers (2006) reported that its sensitivity to detect preeclampsia ranged from 0 to 55 percent, and specificity was 77 to 95 percent.

Isolated gestational proteinuria is a risk factor for preeclampsia (Jayaballa, 2015; Morgan, 2016; Yamada, 2016). As a predictive test for preeclampsia, microalbuminuria has sensitivities that range from 7 to 90 percent and specificities that span 29 to 97 percent (Conde-Agudelo, 2015).

Endothelial Dysfunction and Oxidant Stress

Endothelial activation and inflammation are major participants in the pathophysiology of the preeclampsia syndrome. As a result, compounds such as those listed in Table 40-5 are found to be elevated in circulating blood of affected women, and some have been assessed for their predictive value.

First, fibronectins are high-molecular-weight glycoproteins released from endothelial cells and extracellular matrix following endothelial injury. However, in one systematic review, neither cellular nor total fibronectin levels were clinically useful to predict preeclampsia (Leeflang, 2007).

Thrombocytopenia and platelet dysfunction are integral features of preeclampsia. Platelet activation causes augmented destruction and lower concentrations. Mean platelet volume rises because of platelet immaturity (Kenny, 2015). Although markers of coagulation activation, described earlier (Maternal Thrombocytopenia), are elevated, the substantive overlap with levels in normotensive pregnant women stultifies their predictive value.

Markers of oxidative stress were also hoped to predict preeclampsia. Namely, associated higher levels of lipid peroxides coupled with decreased antioxidant activity raised this possibility. Other markers include iron, transferrin, and ferritin; resistin; hyperhomocysteinemia; blood lipids, including triglycerides, free fatty acids, and lipoproteins; and antioxidants such as ascorbic acid and vitamin E (Christiansen, 2015; Conde-Agudelo, 2015; D'Anna, 2004; Mackay, 2012; Mignini, 2005). However, these have not been found to be predictive.

Last, an imbalance in antiangiogenic factors is linked to preeclampsia etiopathogenesis. For example, serum levels of VEGF and PlGF begin to drop before clinical preeclampsia develops. And, recall from Figure 40-4 that at the same time, levels of some antiangiogenic factors, such as sFlt-1 and sEng, begin to rise (Karumanchi, 2016a; Maynard, 2008). With some of these factors, sensitivities for all cases of preeclampsia ranged from 30 to 50 percent, and specificity approximated 90 percent (Conde-Agudelo, 2015). Their predictive accuracy is higher for early-onset preeclampsia (Redman, 2015b; Tsiakkas, 2016). Determination of the sFlt-1/PlGF ratio in women admitted near 37 weeks' gestation to exclude preeclampsia was useful as a predictive factor (Baltajian, 2016; Zeisler, 2016a,b). These results suggest a clinical role for preeclampsia prediction, especially later in pregnancy (Duckworth, 2016; Gallo, 2016). They may also predict adverse pregnancy outcomes in women with lupus and comorbid antiphospholipid antibodies (Kim, 2016).

Other Markers

As discussed in Chapter 13 (Fetal DNA in the Maternal Circulation), cell-free DNA (cfDNA) can be detected in maternal plasma. It is hypothesized that cfDNA is released in preeclampsia by accelerated apoptosis of cytotrophoblasts (DiFederico, 1999). One MFMU Network study found no correlation between total cfDNA levels and preeclampsia (Silver, 2017).

Proteomic, metabolomic, and transcriptomic technologies can be employed to study serum and urinary proteins and cellular metabolites. These have opened new vistas for preeclampsia prediction, and preliminary studies indicate that these may become useful (Bahado-Singh, 2013; Carty, 2011; Ma, 2014; Myers, 2013).

PREVENTION

Various strategies used to prevent or modify preeclampsia severity have been evaluated. Some are listed in Table 40-6. In general, none of these has been found to be convincingly and reproducibly effective.

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TABLE 40-6

Some Methods to Prevent Preeclampsia That Have Been Evaluated in Randomized Trials

Dietary manipulation—low-salt diet, calcium or fish oil supplementation
Exercise—physical activity, stretching
Cardiovascular drugs—diuretics, antihypertensive drugs
Antioxidants—ascorbic acid (vitamin C), α-tocopherol (vitamin E), vitamin D
Antithrombotic drugs—low-dose aspirin, aspirin/dipyridamole, aspirin + heparin, aspirin + ketanserin

Modified from Staff, 2015.

Dietary and Lifestyle Modifications

Dietary "treatment" for preeclampsia has produced some interesting abuses (Chesley, 1978). A *low-salt diet* was one of the earliest research efforts to prevent preeclampsia (De Snoo, 1937). This was followed by years of inappropriate diuretic therapy. Although these practices were discarded, it ironically was not until relatively recently that the first randomized trial was done and showed that a sodium-restricted diet was ineffective in preventing preeclampsia (Knuist, 1998).

Regular exercise during pregnancy is linked to a lower risk of developing preeclampsia (Barakat, 2016; Morris, 2017). Also, in one systematic review, a trend toward risk reduction with exercise was noted (Kasawara, 2012). Only a few studies have been randomized, and thus, more research is needed (Staff, 2015).

Somewhat related, Abenhaim and coworkers (2008) reported a retrospective cohort study of 677 nonhypertensive women hospitalized for bed rest because of threatened preterm delivery. When outcomes of these women were compared with those of the general obstetrical population, bed rest was associated with a significantly reduced relative risk—0.27—of developing preeclampsia. From two small randomized trials, prophylactic bed rest for 4 to 6 hours daily at home was successful in significantly lowering the incidence of preeclampsia in women with normal blood pressures (Meher, 2006).

Calcium supplementation has been studied in several trials, including one by the National Institute of Child Health and Human Development (NICHD) that included more than 4500 low-risk nulliparas (Levine, 1997). Calcium supplementation did not prevent preeclampsia or pregnancy-associated hypertension. In one metaanalysis, increased calcium intake in high-risk women lowered the risk for preeclampsia (Patrelli, 2012). However, in aggregate, most of these trials have shown that unless women are calcium deficient, supplementation has no salutary effects (Sanchez-Ramos, 2017; Staff, 2015).

Cardioprotective fatty acids found in some fatty fishes are plentiful in diets of Scandinavians and American Eskimos. Because supplementation with these fatty acids likely prevents inflammatory-mediated atherogenesis, it was posited that they might also prevent preeclampsia. Unfortunately, randomized trials conducted thus far have shown no such benefits from fish oil supplementation (Makrides, 2006; Olafsdottir, 2006; Zhou, 2012).

Antihypertensive Drugs

Because of the putative effects of sodium restriction for preeclampsia prevention, diuretic therapy became popular with the introduction of chlorothiazide in 1957 (Finnerty, 1958; Flowers, 1962). In one metaanalysis of nine randomized trials with more than 7000 pregnancies, women given diuretics had a lower incidence of edema and hypertension but not of preeclampsia (Churchill, 2007). Because women with chronic hypertension are at high risk for preeclampsia, several randomized trials have evaluated various antihypertensive drugs to reduce the incidence of superimposed preeclampsia (Chap. 50, Management During Pregnancy). A critical analysis of these trials by Staff and coworkers (2015) failed to demonstrate benefits for this goal.

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Antioxidants

Data imply that an imbalance between oxidant and antioxidant activity plays a role in preeclampsia pathogenesis. Thus, naturally occurring antioxidants—vitamins C, D, and E—might reduce such oxidation. Several randomized studies have assessed antioxidant vitamin supplementation for women at high risk for preeclampsia (Poston, 2006; Rumbold, 2006; Villar, 2009). The Combined Antioxidant and Preeclampsia Prediction Studies (CAPPS) by the MFMU Network included almost 10,000 low-risk nulliparas (Roberts, 2010). None of these studies showed reduced preeclampsia rates in women provided vitamins C and E compared with those given placebo.

Statins were proposed to prevent preeclampsia because they stimulate hemoxygenase-1 expression, which inhibits sFlt-1 release. Preliminary animal data suggest that statins may prevent hypertensive disorders of pregnancy (Lewis, 2017). The MFMU Network plans a randomized trial to test pravastatin for this purpose (Costantine, 2013, 2016).

Metformin inhibits *hypoxic inducible factor 1α* by lowering mitochondrial electron transport chain activity. It reduces sFlt-1 and sEng activity and thus has potential to prevent preeclampsia (Brownfoot, 2016). However, clinical studies are lacking.

Antithrombotic Agents

As noted earlier (Pathogenesis), preeclampsia is characterized by vasospasm, endothelial cell dysfunction, and inflammation, as well as activation of platelets and the coagulation-hemostasis system. Other sequelae include placental infarction and spiral artery thrombosis (Nelson, 2014b). Thus, antithrombotic agents have been evaluated to reduce the incidence of preeclampsia.

Low-molecular-weight heparin for prophylaxis has been studied in several randomized trials. Rodger and colleagues (2016) performed a metaanalysis using individual patient data from 963 women. The risk for recurrent preeclampsia, abruption, or fetal-growth restriction was similar in women receiving heparin or placebo.

Aspirin, in low oral doses of 50 to 150 mg daily, effectively inhibits platelet thromboxane A_2 biosynthesis but has minimal effects on vascular prostacyclin production (Wallenburg, 1986). Still, several clinical trials have shown limited benefits in preeclampsia prevention. For example, a randomized trial from the MFMU Network found that risks for adverse outcomes were not significantly reduced with aspirin therapy (Caritis, 1998). Some combined reports, however, are more favorable. The Paris Collaborative Group performed a metaanalysis that included 31 randomized trials involving 32,217 women (Askie, 2007). For women assigned to receive antiplatelet agents, the relative risk for preeclampsia, superimposed preeclampsia, preterm delivery, or any adverse pregnancy outcome was significantly decreased by 10 percent. Other metaanalyses report marginal benefits of low-dose aspirin for prevention of severe preeclampsia (Roberge, 2012; Villa, 2013). Recently, one randomized trial of more than 1600 women at high risk for preterm preeclampsia provided low-dose aspirin from 11 to 14 weeks' gestation until 36 weeks to prevent recurrence. The rate of preterm recurrence was 1.6 percent in the aspirin group compared with 4.3 percent in the placebo arm (Rolnik, 2017).

In recent dueling metaanalyses, Roberge and colleagues (2017) found that aspirin prophylaxis initiated before 16 weeks' gestation was associated with a significant risk reduction—about 60 percent–for preeclampsia and fetal-growth restriction. Moreover, they found a dose-response effect. At the same time, Meher and associates (2017) performed an individual participant data metaanalysis and reported a much lower—about 10 percent—risk reduction that was significant whether therapy was initiated before or after 16 weeks.

Meanwhile, the U.S. Preventive Services Task Force recommends low-dose aspirin prophylaxis for women at high risk for preeclampsia (Henderson, 2014). Because of this, the American College of Obstetricians and Gynecologists (2016b) issued a Practice Advisory that recommends low-dose aspirin be given between 12 and 28 weeks' gestation to help prevent preeclampsia in high-risk women. This includes those with a history of preeclampsia and those with twins, chronic hypertension, overt diabetes, renal disease, and autoimmune disorders. These results have also raised the question as to whether *all* pregnant women should be given aspirin (Mone, 2017). At this time, our answer is "no."

Low-dose aspirin coupled with heparin mitigates thrombotic sequelae in women with lupus anticoagulant (Chap. 59, Adverse Pregnancy Outcomes). Because of a similarly high prevalence of placental thrombotic lesions found with severe preeclampsia, trials have assessed the possible merits of such treatments for women with prior preeclampsia. In two randomized trials, women with a history of early-onset preeclampsia were given an aspirin therapy or an enoxaparin plus aspirin regimen (Groom, 2017; Haddad, 2016). Outcomes were similar. From their reviews, Sergis and associates (2006) reported better pregnancy outcomes in women with prior severe preeclampsia given low-molecular-weight heparin plus low-dose aspirin compared

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with those given low-dose aspirin alone. Similar findings were reported by de Vries and coworkers (2012).

PREECLAMPSIA

Pregnancy complicated by gestational hypertension is managed based on its severity, presence of preeclampsia, and gestational age. Preeclampsia cannot always be diagnosed definitively. Thus, the Task Force (2013) recommends more frequent prenatal visits if preeclampsia is "suspected." *Increases in systolic and diastolic blood pressure can be either normal physiological changes or signs of developing pathology*. Heightened surveillance permits more prompt recognition of ominous changes in blood pressure, critical laboratory findings, and clinical signs and symptoms (Macdonald-Wallis, 2015).

The basic management objectives for any pregnancy complicated by preeclampsia are: (1) termination of pregnancy with the least possible trauma to mother and fetus, (2) birth of a healthy newborn that subsequently thrives, and (3) complete restoration of health to the mother. In many women with preeclampsia, especially those at or near term, all three objectives are served equally well by induction of labor. *One of the most important clinical questions for successful management is precise knowledge of fetal age.*

Early Diagnosis of Preeclampsia

Traditionally, the frequency of prenatal visits is increased during the third trimester, and this aids early detection of preeclampsia. *Women without overt hypertension, but in whom early developing preeclampsia is suspected during routine prenatal visits, are seen more frequently.* For many years at Parkland Hospital, women with new-onset diastolic blood pressures >80 mm Hg but <90 mm Hg or with sudden abnormal weight gain of more than 2 pounds per week have, at minimum, returned for visits at 7-day intervals. Outpatient surveillance is continued unless overt hypertension, proteinuria, headache, visual disturbances, or epigastric pain supervenes.

Women with overt new-onset hypertension—either diastolic pressures ≥90 mm Hg or systolic pressures ≥140 mm Hg—are admitted to determine if the increase is due to preeclampsia, and if so, to evaluate its severity.

Evaluation

With hospitalization, a systematic evaluation is instituted to include:

- Detailed examination, which is coupled with daily scrutiny for clinical findings such as headache, visual disturbances, epigastric pain, and rapid weight gain
- Daily weight measurement
- Quantification of proteinuria or urine protein:creatinine ratio on admittance and at least every 2 days thereafter
- Blood pressure readings with an appropriate-size cuff every 4 hours, except between 2400 and 0600 unless previous readings are elevated
- Measurements of plasma or serum creatinine and hepatic transaminase levels and a hemogram that includes a platelet count. The frequency of testing is determined by hypertension severity. Although some recommend measurement of serum uric acid and lactate dehydrogenase levels and coagulation studies, their value has been questioned (Conde-Agudelo, 2015; Thangaratinam, 2006).
- Evaluation of fetal size and well-being and amnionic fluid volume, by either physical examination or sonography.

Reduced physical activity throughout much of the day is likely beneficial, but as the 2013 Task Force concluded, absolute bed rest is not desirable. Ample protein and calories are included in the diet, and sodium and fluid intake are not limited or forced.

In sum, goals of evaluation include early identification of preeclampsia or worsening of the syndrome and development of a management plan for timely delivery. Fortunately, many cases are sufficiently mild and near enough to term that they can be managed conservatively until labor commences spontaneously or until the cervix becomes favorable for labor induction. *Complete abatement of all signs and symptoms, however, is uncommon until after delivery*. If severe preeclampsia is diagnosed using the criteria in Table 40-2, further management is subsequently described.

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Consideration for Delivery

Termination of pregnancy is the only cure for preeclampsia. Headache, visual disturbances, or epigastric pain are indicative that convulsions may be imminent, and oliguria is another ominous sign. Severe preeclampsia demands anticonvulsant and often antihypertensive therapy, followed by delivery. Treatment for eclampsia is identical. The prime objectives are to forestall convulsions, to prevent intracranial hemorrhage and serious damage to other vital organs, and to deliver a healthy newborn.

This is true even when the cervix is unfavorable (Tajik, 2012). Labor induction is carried out, usually with preinduction cervical ripening with a prostaglandin or osmotic dilator (Chap. 26, Preinduction Cervical Ripening).

Concerns stemming from an unfavorable cervix, a perceived sense of urgency because of preeclampsia severity, and a need to coordinate neonatal intensive care have led some to advocate cesarean delivery. Alexander and colleagues (1999) reviewed 278 singleton liveborn neonates weighing 750 to 1500 g delivered of women with severe preeclampsia at Parkland Hospital. In half of the women, labor was induced, and the remainder underwent cesarean delivery without labor. Induction was successful in accomplishing vaginal delivery in a third, and it was not harmful to very-low-birthweight neonates. Others have reported similar observations (Alanis, 2008; Roland, 2017). However, whenever it appears that induction almost certainly will not succeed or attempts have failed, then cesarean delivery is indicated.

For a woman near term, with a soft, partially effaced cervix, even a milder degree of preeclampsia probably carries more risk to the mother and her fetus-newborn than does induction of labor (Tajik, 2012). A randomized trial of 756 women with mild preeclampsia supported delivery after 37 weeks' gestation (Koopmans, 2009).

When the fetus is preterm, the tendency is to temporize in the hope that additional weeks in utero will reduce the risk of neonatal death or serious morbidity from prematurity. Such a policy certainly is justified in milder cases. Assessments of fetal well-being and placental function are performed, especially when the fetus is immature. Most recommend frequent performance of nonstress testing or biophysical profiles to assess fetal well-being (American College of Obstetricians and Gynecologists, 2016a). Several tests can be used to provide evidence of lung maturity (Chap. 34, Necrotizing Enterocolitis). An sFlt-1/PlGF ratio <38 is predictive of the short-term absence of preeclampsia, but this ratio testing is still investigational (Zeisler, 2016a,b). Also, women with higher ratios tend to have more adverse outcomes (Baltajian, 2016).

The decision to deliver late-preterm fetuses is less clear. Barton and coworkers (2011) reported excessive neonatal morbidity in women delivered before 38 weeks despite having stable, mild, nonproteinuric hypertension. The Netherlands study of 4316 newborns delivered between $34^{0/7}$ and $36^{6/7}$ weeks also described substantive neonatal morbidity in these cases (Langenveld, 2011). Another Dutch study—HYPITAT-II—randomly assigned women with nonsevere hypertension between 34 and 37 weeks to immediate delivery or to expectant management (Broekhuijsen, 2015). Immediate delivery reduced the risks for adverse maternal outcomes—1.1 versus 3.1 percent. However, it increased the risk for neonatal respiratory distress syndrome—5.7 versus 1.7 percent.

Hospitalization versus Outpatient Management

For women with mild-to-moderate stable hypertension—whether or not preeclampsia has been confirmed—monitoring is continued. During surveillance, reduced physical activity throughout much of the day, at least intuitively, seems beneficial. That said, complete bed rest is not recommended by the 2013 Task Force. First, this is pragmatically unachievable because of the severe restrictions it places on otherwise well women. Also, it likely predisposes to thromboembolism (Knight, 2007). To reduce activity, several studies have addressed the benefits of inpatient care and outpatient management.

The concept of prolonged hospitalization for women with hypertension arose during the 1970s. At Parkland Hospital, an inpatient antepartum unit was established in 1973 by Dr. Peggy Whalley in large part to provide care for such women. Initial results from this unit were reported by Hauth (1976) and Gilstrap (1978) and their coworkers. Most hospitalized women have a beneficial response characterized by amelioration or improvement of hypertension. *These women are not "cured," and nearly 90 percent have recurrent hypertension before or during labor.* By 2016, more than 10,000 nulliparas with mild-to-moderate, early-onset hypertension during pregnancy had been managed successfully in this unit. Provider costs—*not charges*—for this relatively simple physical facility, modest nursing care, no drugs other than iron and folate supplements, and few essential laboratory tests are minimal compared with the cost of neonatal intensive care for a preterm neonate. Importantly, none of these women have suffered thromboembolic disease.

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Many clinicians believe that further hospitalization is not warranted if hypertension abates within a few days, and this has legitimized third-party payers to deny hospitalization reimbursement. Consequently, many women with mild-to-moderate hypertension are managed at home. Outpatient management may continue as long as preeclampsia syndrome does not worsen and fetal jeopardy is not suspected. Sedentary activity throughout the greater part of the day is recommended. These women are instructed in detail to report symptoms. Home blood pressure and urine protein monitoring or frequent evaluations by a visiting nurse may prove beneficial.

To assess this approach, 1182 nulliparas with mild gestational hypertension—20 percent had proteinuria—were managed with home health care (Barton, 2002). Their mean gestational ages were 32 to 33 weeks at enrollment and 36 to 37 weeks at delivery. Severe preeclampsia developed in approximately 20 percent, about 3 percent developed HELLP syndrome, and two women had eclampsia. Perinatal outcomes were generally good. In approximately 20 percent, there was fetal-growth restriction, and the perinatal mortality rate was 4.2 per 1000 births.

Several studies have compared continued hospitalization and outpatient care. In a pilot study from Parkland Hospital, 72 nulliparas with new-onset hypertension from 27 to 37 weeks were assigned either to continued hospitalization or to outpatient care (Horsager, 1995). The only significant difference was that women in the home care group developed severe preeclampsia significantly more frequently than hospitalized women—42 versus 25 percent. In another trial, after hospital evaluation, 218 women with mild gestational nonproteinuric hypertension were similarly divided (Crowther, 1992). As shown in Table 40-7, the mean hospital duration was 22.2 days for women with inpatient management compared with only 6.5 days in the home care group. Preterm delivery before 34 and before 37 weeks' gestation was increased twofold in the outpatient group. However, maternal and newborn outcomes were otherwise similar.

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TABLE 40-7

Randomized Clinical Trials Comparing Hospitalization versus Routine Care for Women with Mild Gestational Hypertension or Preeclampsia

	Maternal Characteristics—Admission					Maternal Characteristics—Delivery				Perinatal Outcomes		
Study Groups	No.	$Para_0$ (%)	Chronic HTN (%)	EGA (wk)	Prot (%)	EGA (wk)	<37 wk (%)	< 34 wk (%)	Mean Hosp (d)	Mean BW (g)	SGA (%)	PMR (%)
Crowther (1992)	218[a]											
Hospitalization	110	13	14	35.3	0	38.3	12	1.8	22.2	3080	14	0
Outpatient	108	13	17	34.6	0	38.2	22	3.7	6.5	3060	14	0
Tuffnell (1992)	54											
Day Unit	24	57	23	36	0	39.8	—	—	1.1	3320	—	0
Usual Care	30	54	21	36.5	21	39	—	—	5.1	3340	—	0
Turnbull (2004)	374[b]											
Hospitalization	125	63	0	35.9	22	39	—	—	8.5	3330	3.8	0
Day Unit	249	62	0	36.2	22	39.7	—	—	7.2	3300	2.3	0

[a]Excluded women with proteinuria at study entry.

[b]Included women with ≤1+ proteinuria.

BW = birthweight; EGA = estimated gestational age; HTN = hypertension; $Para_0$= nulliparas; PMR = perinatal mortality rate; Prot = proteinuria; SGA = small for gestational age.

Another approach, popular in Europe, is day care (Milne, 2009). In one study, 54 women with hypertension after 26 weeks' gestation were assigned to either day care or routine outpatient management (see Table 40-7) (Tuffnell, 1992). Progression to overt preeclampsia and labor inductions were significantly greater in the routine outpatient management group. In another, 395 women participated in either day care or inpatient management (Turnbull, 2004). Almost 95 percent had mild-to-moderate hypertension. Of enrolled women, 288 lacked proteinuria, and 86 had ≥1+ proteinuria. There were no perinatal deaths, and none of the women developed eclampsia or HELLP syndrome. Costs for either scheme were not significantly different, and general satisfaction favored day care.

In sum, either inpatient or close outpatient management is appropriate for a woman with mild de novo hypertension, including those with nonsevere preeclampsia. Most of these studies were carried out in academic centers with dedicated management teams. That said, the key to success is close surveillance and a conscientious patient with good home support.

Antihypertensive Therapy for Mild-to-Moderate Hypertension

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The use of antihypertensive drugs to prolong pregnancy or modify perinatal outcomes in pregnancies complicated by various hypertensive disorders has been of considerable interest. Treatment for women with chronic hypertension complicating pregnancy is discussed in detail in Chapter 50 (Management During Pregnancy).

Drug treatment for early mild preeclampsia has been disappointing (Table 40-8). Sibai and colleagues (1987a) reported that women given labetalol had significantly lower mean blood pressures. However, mean pregnancy prolongation, gestational age at delivery, and birthweight did not differ between groups. The cesarean delivery rate and the number of newborns admitted to special-care nurseries were also similar. *The frequency of growth-restricted neonates was doubled in women given labetalol—19 versus 9 percent.* The three other studies listed in Table 40-8 compared labetalol or the calcium-channel blockers nifedipine and isradipine against placebo. Except for fewer episodes of severe hypertension, none of these studies showed any benefits from antihypertensive treatment (Magee, 2015). Similar conclusions were reached by Abalos and associates (2014), who reviewed 49 randomized trials of active antihypertensive therapy compared with either no treatment or placebo given to women with mild-to-moderate gestational hypertension.

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TABLE 40-8

Randomized Placebo-Controlled Trials of Antihypertensive Therapy for Early Mild Gestational Hypertension

Study	Study Drug (No.)	Pregnancy Prolonged (d)	Severe HTN[a] (%)	Cesarean Delivery (%)	Placental Abruption (%)	Mean Birthweight (g)	Growth Restriction (%)	Neonatal Deaths (No.)
Sibai (1987a)[a] 200 inpatients	Labetalol (100)	21.3	5	36	2	2205	19[c]	1
	Placebo (100)	20.1	15[c]	32	0	2260	9	0
Sibai (1992)[b] 200 outpatients	Nifedipine (100)	22.3	9	43	3	2405	8	0
	Placebo (100)	22.5	18[c]	35	2	2510	4	0
Pickles (1992) 144 outpatients	Labetalol (70)	26.6	9	24	NS	NS	NS	NS
	Placebo (74)	23.1	10	26	NS	NS	NS	NS
Wide-Swensson (1995)	Isradipine (54)	23.1	22	26	NS	NS	NS	0
111 outpatients	Placebo (57)	29.8	29	19	NS	NS	NS	0

[a]All women had preeclampsia.

[b]Includes postpartum hypertension.

[c]$p < .05$ when study drug compared with placebo.

HTN = hypertension; NS = not stated.

Delayed Delivery

Up through the early 1990s, the prevailing practice was that women with severe preeclampsia were usually delivered without delay. However, another approach for women with preterm severe preeclampsia has also been advocated. This approach calls for “conservative” or “expectant” management

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with the aim of improving neonatal outcome without compromising maternal safety. Aspects of such management always include careful daily—and usually more frequent—inpatient monitoring of the mother and her fetus.

Expectant Management of Preterm Severe Preeclampsia

Theoretically, antihypertensive therapy has potential application when severe preeclampsia develops before intact neonatal survival is likely. Such management is controversial, and it may be dangerous. In one of the first studies, Sibai and the Memphis group (1985) attempted to prolong pregnancy because of fetal immaturity in 60 women with severe preeclampsia between 18 and 27 weeks. The results were disastrous. *The perinatal mortality rate was 87 percent. Although no mothers died, 13 suffered placental abruption, 10 had eclampsia, three developed renal failure, two had hypertensive encephalopathy, one had an intracerebral hemorrhage, and another had a ruptured hepatic hematoma.*

Because of their early study, the Memphis group redefined criteria and performed a randomized trial of aggressive versus expectant management for 95 women who had severe preeclampsia but with more advanced gestations of 28 to 32 weeks (Sibai, 1994). *Women with HELLP syndrome were excluded from this trial.* Aggressive management included glucocorticoid administration for fetal lung maturation followed by delivery in 48 hours. Expectantly managed women were observed at bed rest and given either labetalol or nifedipine orally for severe hypertension. In this study, pregnancy was prolonged for a mean of 15.4 days in the expectant management group. An overall improvement in neonatal outcomes was also reported.

Following these experiences, expectant management became more commonly practiced, but with the caveat that women with HELLP syndrome or growth-restricted fetuses were usually excluded. But in a subsequent follow-up observational study, the Memphis group compared outcomes in 133 preeclamptic women with and 136 without HELLP syndrome who presented between 24 and 36 weeks (Abramovici, 1999). Women were subdivided into three study groups. The first group included those with *complete HELLP syndrome*. The second group included women with *partial HELLP syndrome*—defined as either one or two but not all three of the defining laboratory values. The third group included women who had severe preeclampsia without HELLP syndrome. Perinatal outcomes were similar in each group, and importantly, outcomes were not improved with procrastination. Despite this, the investigators concluded that women with partial HELLP syndrome and those with severe preeclampsia alone could be managed expectantly. Those with fetal-growth restriction generally have shorter interval-to-delivery durations (McKinney, 2016).

Sibai and Barton (2007b) reviewed expectant management of severe preeclampsia from 24 to 34 weeks. More than 1200 women were included, and although the average time gained ranged from 5 to 10 days, the maternal morbidity rates were formidable. Serious complications in some of these and in later studies included placental abruption, HELLP syndrome, pulmonary edema, renal failure, and eclampsia (Table 40-9). Moreover, perinatal mortality rates averaged 90 per 1000 births. Fetal-growth restriction was common, and in the studies from The Netherlands, it was an astounding 94 percent (Ganzevoort, 2005a,b). Perinatal mortality rates are disproportionately high in these growth-restricted neonates, but maternal outcomes are not appreciably different (Haddad, 2007; Shear, 2005). The MEXPRE Latin Study was a multicenter trial that randomly assigned 267 women with severe preeclampsia at 28 to 32 weeks to prompt delivery or to expectant management (Vigil-De Gracia, 2013). The perinatal mortality rate approximated 9 percent in each group, the composite neonatal morbidity outcome was not improved with expectant management. On the other hand, fetal-growth restriction—22 versus 9 percent—and placental abruption—7.6 versus 1.5 percent—were significantly higher in the group managed expectantly.

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TABLE 40-9

Maternal and Perinatal Outcomes Reported since 2005 with Expectant Management of Severe Preeclampsia from 24 to 34 Weeks

			Maternal Outcomes (%)					Perinatal Outcomes (%)	
Study	No.	Days Gained	Placental Abruption	HELLP	Pulm. Edema	AKI	Eclampsia	FGR	PMR
Oettle (2005)	131[a]	11.6	23	4.6	0.8	2.3	2.3	NS	13.8
Shear (2005)	155	5.3	5.8	27	3.9	NS	1.9	62	3.9
Ganzevoort (2005a, b)	216	11	1.8	18	3.6	NS	1.8	94	18
Bombrys (2009)	66	5	11	8	9	3	0	27	1.5
Abdel-Hady (2010)	211	12	3.3	7.6	0.9	6.6	0.9	NS	48
Vigil-De Gracia (2013)	131	10.3	7.6	14	1.5	4.5	0.8	22	8.7
Range	910	5–12	1.8–23	4.6–27	0.9–3.9	2.3–6.6	0.9–18	27–94	1.5–48

[a]Includes one maternal death.

AKI = acute kidney injury; EGA = estimated gestational age; FGR = fetal-growth restriction; HELLP = hemolysis, elevated liver enzyme levels, low platelet count syndrome; NS = not stated; PMR = perinatal mortality rate; Pulm. = pulmonary.

Expectant Management of Midtrimester Severe Preeclampsia

Several small studies have focused on expectant management of severe preeclampsia syndrome *before 28 weeks*. In their review, Bombrys and coworkers (2008) found eight such studies that included nearly 200 women with severe preeclampsia with an onset <26 completed weeks. Maternal complications were common. Because no neonates survived when delivered before 23 weeks, the Task Force (2013) recommends pregnancy termination in these cases. For women with slightly more advanced pregnancies, however, the decision is less clear. For example, at 23 weeks' gestation, the perinatal survival rate was 18 percent, but long-term perinatal morbidity is yet unknown. For women with pregnancies at 24 to 26 weeks, perinatal survival approached 60 percent, and it averaged almost 90 percent for those at 26 weeks.

At least five observational studies of women with severe midtrimester preeclampsia who were managed expectantly have been published since 2005 (Abdel-Hady, 2010; Belghiti, 2011; Bombrys, 2008; Budden, 2006; Gaugler-Senden, 2006). Maternal complications developed in 60 percent, and there was one maternal death. The perinatal mortality rate was 650 per 1000 births. At this time, no comparative studies attest to perinatal benefits of such expectant treatment versus early delivery in the face of serious maternal complications, which approach rates of 50 percent. We do not recommend such management.

Glucocorticoids for Lung Maturation

To enhance fetal lung maturation, glucocorticoids have been administered to women with severe hypertension who are remote from term. Treatment

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does not seem to worsen maternal hypertension, and a lower incidence of respiratory distress and improved fetal survival rates have been cited. That said, only one randomized trial has evaluated corticosteroids given to hypertensive women for fetal lung maturation. This trial included 218 women with severe preeclampsia between 26 and 34 weeks' gestation who were randomly assigned to betamethasone or placebo administration (Amorim, 1999). Rates of neonatal complications that included respiratory distress, intraventricular hemorrhage, and death were reduced significantly when betamethasone was given compared with placebo. *On the heavily weighted negative side, there were two maternal deaths and 18 stillbirths.* We add these findings to buttress our unenthusiastic acceptance of attempts to prolong gestation in many of these women (Alexander, 2015; Bloom, 2003).

Expectant Management Recommendations

Taken in toto, these studies do not show overwhelming benefits compared with maternal risks for expectant management of severe preeclampsia in women with gestations from 24 to 32 weeks. Despite these caveats, the Society for Maternal-Fetal Medicine (2011) has determined that such management is a reasonable alternative in selected women with severe preeclampsia before 34 weeks (Fig. 40-14). The Task Force (2013) supports this recommendation. As shown in Table 40-10, such management calls for in-hospital maternal and fetal surveillance with delivery prompted by evidence for worsening severe preeclampsia or maternal or fetal compromise. Although attempts are made for vaginal delivery in most cases, the likelihood of cesarean delivery rises with decreasing gestational age.

FIGURE 40-14

Clinical management algorithm for severe preeclampsia at <34 weeks. HELLP = hemolysis, elevated liver enzyme levels, low platelet count; L&D = labor and delivery; $MgSO_4$= magnesium sulfate; UOP = urine output. (Adapted from the Society for Maternal-Fetal Medicine, 2011.)

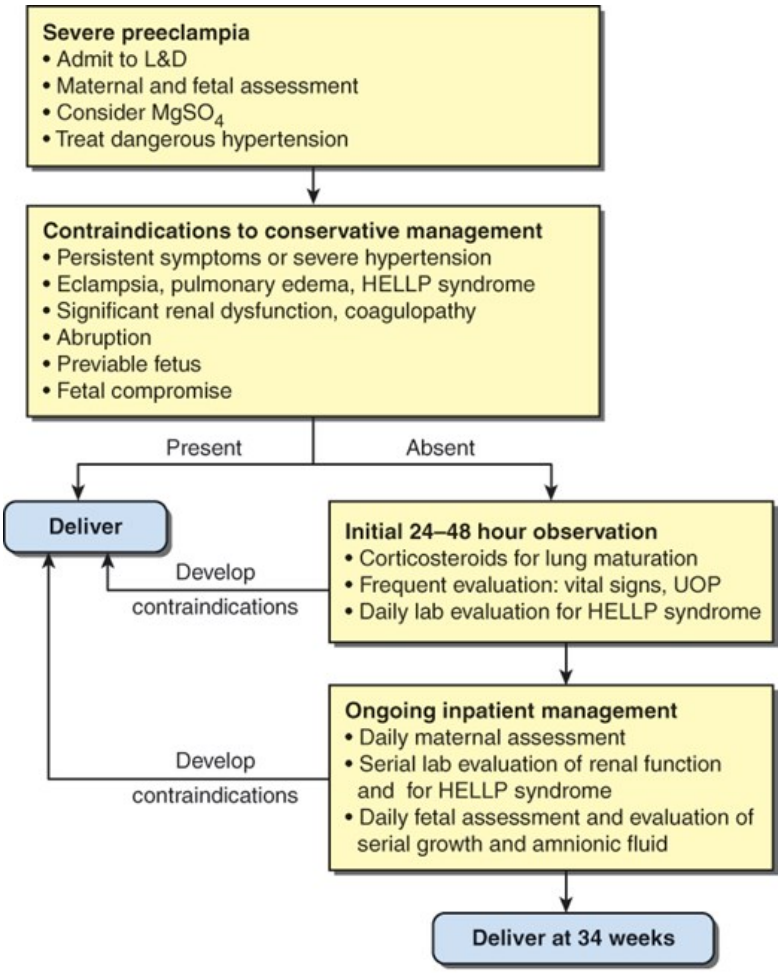

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TABLE 40-10

Indications for Delivery in Women <34 Weeks' Gestation Managed Expectantly

Corticosteroid Therapy for Lung Maturation[a] and Delivery after Maternal Stabilization:
Uncontrolled severe hypertension
Eclampsia
Pulmonary edema
Placental abruption
Disseminated intravascular coagulation
Nonreassuring fetal status
Fetal demise
Corticosteroid Therapy for Lung Maturation—Delay Delivery 48 hr If Possible:
Preterm ruptured membranes or labor
Thrombocytopenia <100,000/μL
Hepatic transaminase levels twice upper limit of normal
Fetal-growth restriction
Oligohydramnios
Reversed end-diastolic Doppler flow in umbilical artery
Worsening renal dysfunction

[a]Initial dose only, do not delay delivery.

From the Society for Maternal-Fetal Medicine, 2011, and the Task Force of the American College of Obstetricians and Gynecologists, 2013.

Our view is more conservative. Undoubtedly, the overriding reason to terminate pregnancies with severe preeclampsia is maternal safety. Indeed, it seems obvious that a delay to prolong gestation in women with severe preeclampsia may have serious maternal consequences (see Table 40-9). These observations are even more pertinent when considered with the absence of convincing evidence that perinatal outcomes are markedly improved by the average prolongation of pregnancy by approximately 1 week. If undertaken, the caveats that mandate delivery shown in Table 40-10 should be strictly heeded.

Corticosteroids to Ameliorate HELLP Syndrome

At least three randomized trials have evaluated the benefits of glucocorticoids given to improve the laboratory abnormalities associated with HELLP syndrome. First, Fonseca and associates (2005) randomly assigned 132 women with HELLP syndrome to either dexamethasone or placebo administration. Outcomes assessed included hospitalization length, recovery time of abnormal laboratory test results, resolution of clinical parameters, and complications that included acute renal failure, pulmonary edema, eclampsia, and death. None of these was significantly different between the two groups. In another study, 105 postpartum women with HELLP syndrome were assigned to dexamethasone or placebo treatment (Katz, 2008). Outcomes were analyzed similarly to the Fonseca study, and no advantage to dexamethasone was found (Fig. 40-15). In the third study, preeclamptic women were given either placebo or methylprednisolone if their platelet count was between 50,000 and 150,000/μL (Pourrat, 2016). No benefits were gained from corticosteroid therapy. Because of these findings, the 2013 Task Force does not recommend corticosteroid treatment for thrombocytopenia with HELLP syndrome.

FIGURE 40-15

Recovery times for platelet counts and serum aspartate transaminase (AST) levels in women with HELLP syndrome assigned to receive treatment with dexamethasone or placebo. (Data from Katz, 2008.)

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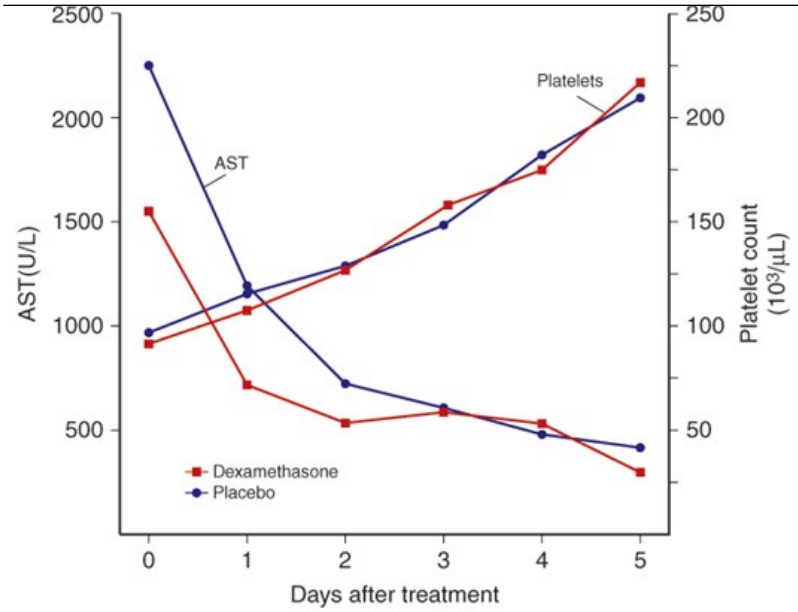

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Experimental Therapies

In several preliminary studies, therapies have attempted to lower serum levels or mitigate the action of antiangiogenic factors. Some of these include *therapeutic apheresis*, done to lower sFlt-1 levels (Thadhani, 2016). *Pravastatin* has been given for preeclampsia prevention (Cleary, 2014). *Sildenafil citrate*, a phosphodiesterase inhibitor, has been provided to promote vasodilation (Trapani, 2016; Vigil-De Gracia, 2016). In a recent randomized trial of 120 women with early-onset preeclampsia, an *recombinant antithrombin infusion* compared with saline afforded the same interval-to-delivery timing (Sibai, 2017).

ECLAMPSIA

Preeclampsia complicated by generalized tonic-clonic convulsions appreciably raises the risk to both mother and fetus. In an earlier report, Mattar and Sibai (2000) described outcomes in 399 consecutive women with eclampsia from 1977 through 1998. Major maternal complications included placental abruption—10 percent, neurological deficits—7 percent, aspiration pneumonia—7 percent, pulmonary edema—5 percent, cardiopulmonary arrest—4 percent, and acute renal failure— 4 percent. Moreover, 1 percent of these women died. Several subsequent reports similarly described excessive maternal morbidity and mortality rates with eclampsia that also included HELLP syndrome, pulmonary embolism, and stroke (Andersgaard, 2006; Knight, 2007). In The Netherlands, there were three maternal deaths among 222 eclamptic women (Zwart, 2008). Data from Ireland and Australia are similar (O'Connor, 2013; Thornton, 2013). In perspective, this is a thousand-fold increase above the overall maternal death rates for these countries.

Almost without exception—but at times unnoticed—preeclampsia precedes the convulsion onset. Eclampsia is most common in the last trimester and becomes increasingly frequent as term approaches. In more recent years, the incidence of postpartum eclampsia has declined. This is presumably related to improved access to prenatal care, earlier detection of antepartum preeclampsia, and prophylactic use of magnesium sulfate (Chames, 2002). Importantly, other diagnoses should be considered in women with convulsions more than 48 hours postpartum or in women with focal neurological deficits, prolonged coma, or atypical eclampsia (Sibai, 2012).

Clinical Findings with Eclampsia

Eclamptic seizures may be violent, and the woman must be protected, especially her airway. So forceful are the muscular movements that the woman may throw herself out of her bed, and if not protected, her tongue is bitten by the violent action of the jaws (Fig. 40-16). This phase, in which the muscles alternately contract and relax, may last approximately a minute. Gradually, the muscular movements become smaller and less frequent, and finally the woman lies motionless.

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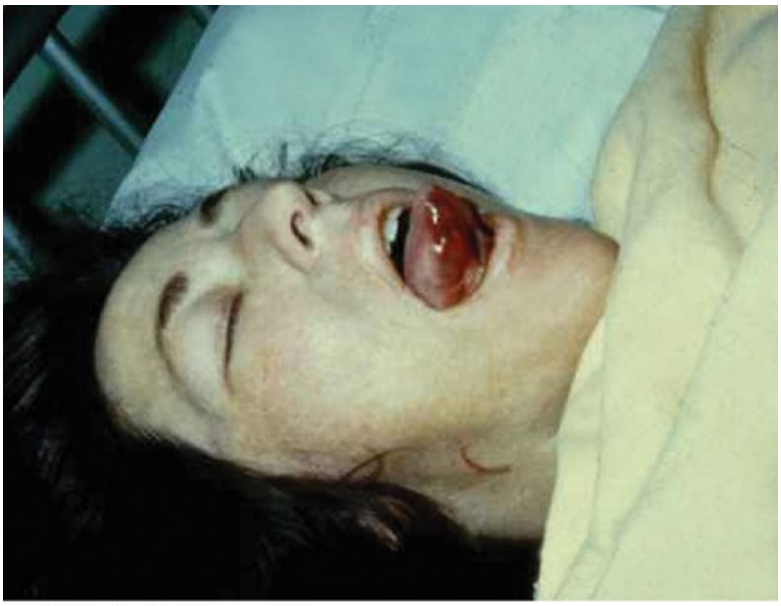
FIGURE 40-16

Hematoma of tongue from laceration during an eclamptic convulsion. Thrombocytopenia may have contributed to the bleeding.



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After a seizure, the woman is postictal, but in some, a coma of variable duration ensues. When the convulsions are infrequent, the woman usually recovers some degree of consciousness after each attack. As the woman arouses, a semiconscious combative state may ensue. In severe cases, coma persists from one convulsion to another, and death may result. In rare instances, a single convulsion may be followed by coma from which the woman may never emerge. As a rule, however, death does not occur until after frequent convulsions. Finally and also rarely, convulsions continue unabated—*status epilepticus*—and require deep sedation and even general anesthesia to obviate anoxic encephalopathy.

The respiratory rate after an eclamptic convulsion is usually increased and may reach 50 or more per minute in response to hypercarbia, lactic acidemia, and transient hypoxia. Cyanosis may be observed in severe cases. High fever is a grave sign as it likely emanates from cerebrovascular hemorrhage.

Proteinuria is usually, but not always, present as discussed earlier (Kidney). Urine output may be diminished appreciably, and occasionally anuria develops. There may be hemoglobinuria, but hemoglobinemia is rare. Often, facial and peripheral edema is pronounced, but it may be absent (Fig. 40-17).

FIGURE 40-17

Severe edema in a young nullipara with antepartum preeclampsia. (Used with permission from Dr. Nidhi Shah.)

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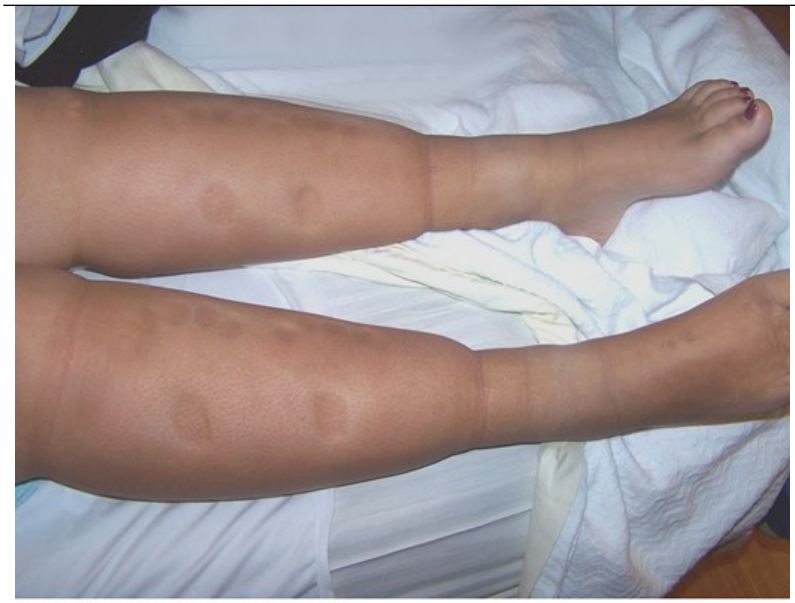

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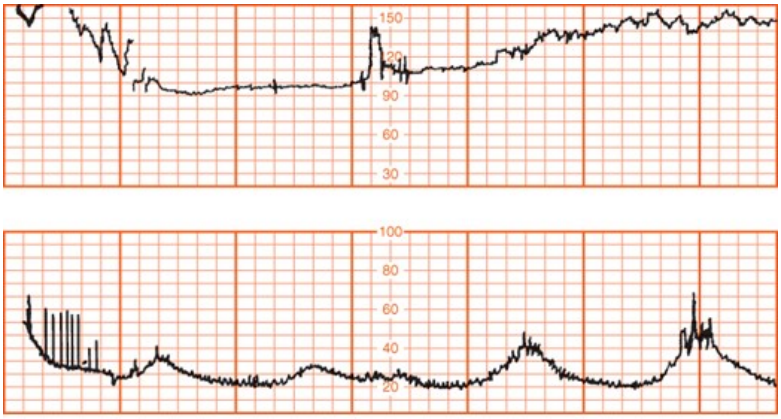
As with severe preeclampsia, urinary output rises after delivery and is usually an early sign of improvement. With renal dysfunction, serum creatinine levels are serially monitored. Proteinuria and edema ordinarily disappear within a week postpartum. In most cases, blood pressure returns to normal within a few days to 2 weeks after delivery (Berks, 2009). As subsequently discussed, persisting and severe hypertension likely predicts underlying chronic vascular disease (Podymow, 2010).

In antepartum eclampsia, labor may begin spontaneously shortly after convulsions ensue and may progress rapidly. If the convulsions occur during labor, contractions may increase in frequency and intensity, and the duration of labor may be shortened. Because of maternal hypoxemia and lactic acidemia caused by convulsions, fetal bradycardia often follows a seizure (Fig. 40-18). The fetal heart rate usually recovers within 2 to 10 minutes (Ambia, 2018). If it persists more than about 10 minutes, another cause of bradycardia, such as placental abruption or imminent delivery, should be considered.

FIGURE 40-18

Fetal heart rate tracing shows fetal bradycardia following an intrapartum eclamptic convulsion. Bradycardia resolved and beat-to-beat variability returned approximately 5 minutes following the seizure.



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Pulmonary edema may follow shortly after eclamptic convulsions or up to several hours later. This usually is caused by aspiration pneumonitis from gastric-content inhalation during vomiting that frequently accompanies convulsions. In some women, pulmonary edema may be caused by ventricular failure from increased afterload that results from severe hypertension. Both pulmonary edema and hypertension can be further aggravated by

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vigorous intravenous fluid administration (Dennis, 2012b). Such pulmonary edema from ventricular failure is more common in morbidly obese women and in those with previously unappreciated chronic hypertension.

Occasionally, sudden death occurs synchronously with an eclamptic convulsion, or it follows shortly thereafter. Most often in these cases, a massive cerebral hemorrhage is the cause (see Fig. 40-10). Hemiplegia may result from sublethal hemorrhage. Cerebral hemorrhages are more likely in older women with underlying chronic hypertension.

In approximately 10 percent of eclamptic women, some degree of blindness follows a seizure. The causes of blindness or impaired vision were discussed earlier (Uteroplacental Perfusion). Blindness with severe preeclampsia without convulsions usually stems from retinal detachment (Vigil-De Gracia, 2011). Conversely, blindness with eclampsia is typically due to occipital lobe edema (Cunningham, 1995). In both instances, however, the prognosis for return to normal function is good and is usually complete within 1 to 2 weeks postpartum.

Up to 5 percent of women with eclampsia have substantively altered consciousness, including persistent coma, following a seizure. This is due to extensive cerebral edema, and associated transtentorial herniation may cause death (Cerebrovascular Pathophysiology).

Rarely, eclampsia is followed by psychosis, and the woman becomes violent. This may last for several days to 2 weeks. The prognosis for return to normal function is good, provided there was no preexisting mental illness. It is presumed to be similar to postpartum psychosis discussed in Chapter 61 (Anxiety Disorders). Antipsychotic medications have proven effective in the few cases of posteclampsia psychosis treated at Parkland Hospital.

Generally, eclampsia is more likely to be diagnosed too frequently rather than overlooked. Epilepsy, encephalitis, meningitis, brain tumor, neurocysticercosis, amnionic fluid embolism, postdural puncture cephalalgia, and ruptured cerebral aneurysm during late pregnancy or in the puerperium may simulate eclampsia. Until other such causes are excluded, however, all pregnant women with convulsions should be considered to have eclampsia.

Management of Eclampsia

Magnesium sulfate is highly effective to prevent convulsions in women with preeclampsia and to stop them in those with eclampsia. In his review, Chesley (1978) cited observational data by Pritchard and colleagues (1955, 1975) from Parkland Hospital and from his own institution. At that time, most eclampsia regimens in the United States adhered to a similar philosophy, and it is still in use today:

1. Control of convulsions using an intravenously administered loading dose of magnesium sulfate that is followed by a maintenance dose, usually intravenous, of magnesium sulfate
2. Intermittent administration of an antihypertensive medication to lower blood pressure whenever it is considered dangerously high
3. Avoidance of diuretics unless pulmonary edema is obvious, limitation of intravenous fluid administration unless fluid loss is excessive, and avoidance of hyperosmotic agents
4. Delivery of the fetus to resolve preeclampsia.

Magnesium Sulfate to Control Convulsions

Magnesium sulfate administered parenterally is an effective anticonvulsant that avoids producing central nervous system depression. It may be given intravenously by continuous infusion or intramuscularly by intermittent injection (Table 40-11). The dosages for severe preeclampsia are the same as for eclampsia. Because labor and delivery is a more likely time for convulsions to develop, women with preeclampsia-eclampsia usually are given magnesium sulfate during labor and for 24 hours postpartum.

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TABLE 40-11

Magnesium Sulfate Dosage Schedule for Severe Preeclampsia and Eclampsia

Continuous Intravenous (IV) Infusion
Give 4- to 6-g loading dose of magnesium sulfate diluted in 100 mL of IV fluid administered over 15–20 min Begin 2 g/hr in 100 mL of IV maintenance infusion. Some recommend 1 g/hr Monitor for magnesium toxicity: Assess deep tendon reflexes periodically Some measure serum magnesium level at 4–6 hr and adjust infusion to maintain levels between 4 and 7 mEq/L (4.8 to 8.4 mg/dL) Measure serum magnesium levels if serum creatinine ≥1.0 mg/dL Magnesium sulfate is discontinued 24 hr after delivery
Intermittent Intramuscular Injections
Give 4 g of magnesium sulfate ($MgSO_4 \cdot 7H_2O$ USP) as a 20% solution intravenously at a rate not to exceed 1 g/min Follow promptly with 10 g of 50% magnesium sulfate solution, one half (5 g) injected deeply in the upper outer quadrant of each buttock through a 3-inch-long 20-gauge needle. (Addition of 1.0 mL of 2% lidocaine minimizes discomfort.) If convulsions persist after 15 min, give up to 2 g more intravenously as a 20% solution at a rate not to exceed 1 g/min. If the woman is large, up to 4 g may be given slowly. Every 4 hr thereafter, give 5 g of a 50% solution of magnesium sulfate injected deeply in the upper outer quadrant of alternate buttocks, but only after ensuring that: The patellar reflex is present, Respirations are not depressed, and Urine output the previous 4 hr exceeded 100 mL Magnesium sulfate is discontinued 24 hr after delivery

In the United States, magnesium sulfate is almost universally administered intravenously. Of concern, magnesium sulfate solutions, although inexpensive to prepare, are not readily available in all parts of the developing world. And even when the solutions are available, the technology to infuse them may not be. Therefore, it should not be overlooked that the drug can be administered intramuscularly and that this route is as effective as intravenous administration (Salinger, 2013). In two reports from India, intramuscular regimens were nearly equivalent in preventing recurrent convulsions and maternal deaths in women with eclampsia (Chowdhury, 2009; Jana, 2013). These observations comport with earlier ones from Parkland Hospital (Pritchard, 1975, 1984).

Magnesium sulfate is not given to treat hypertension. Magnesium most likely exerts a specific anticonvulsant action on the cerebral cortex. Typically, the mother stops convulsing after the initial 4-g loading dose. By an hour or two, she regains consciousness sufficiently to be oriented to place and time.

The magnesium sulfate dosage regimens presented in Table 40-11 usually result in plasma magnesium levels illustrated in Figure 40-19. When magnesium sulfate is given to arrest eclamptic seizures, 10 to 15 percent of women will have a subsequent convulsion. If so, an additional 2-g dose of magnesium sulfate in a 20-percent solution is slowly administered intravenously. In a small woman, this additional 2-g dose may be used once, but it can be given twice if needed in a larger woman. In only 5 of 245 women with eclampsia at Parkland Hospital was it necessary to use alternative supplementary anticonvulsant medication to control convulsions (Pritchard, 1984). For these, an intravenous barbiturate is given slowly. Midazolam or lorazepam may also be given in a small single dose, but prolonged use is avoided because it is associated with a higher mortality rate from aspiration pneumonia (Royal College of Obstetricians and Gynaecologists, 2006).

FIGURE 40-19

Serum magnesium concentration in normotensive and preeclamptic women following a 4-g loading dose of magnesium sulfate and 2 g/h infusion. (Data from Brookfield, 2016.)

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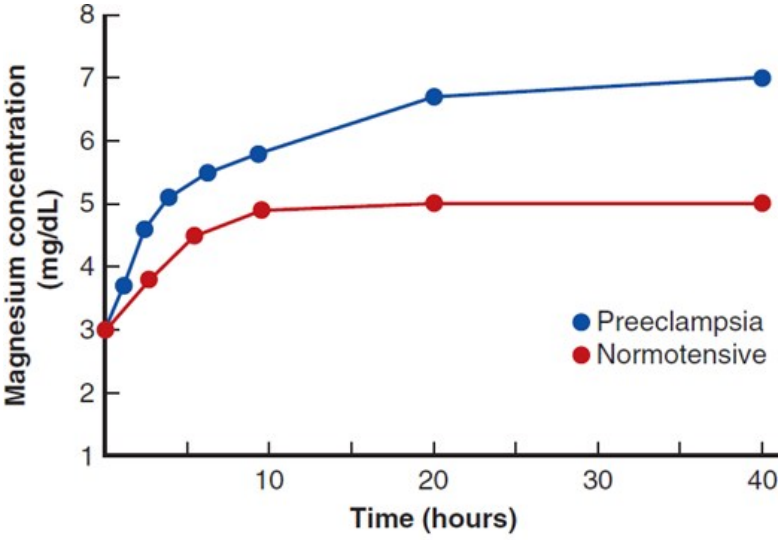

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Maintenance magnesium sulfate therapy has traditionally been continued for 24 hours after delivery. For eclampsia that develops postpartum, magnesium sulfate is administered for 24 hours after the onset of convulsions. A few investigators have truncated this therapy duration to 12 hours and found no seizures (Anjum, 2016; Ehrenberg, 2006; Kashanian, 2016). And more recently, Ludmir and colleagues (2017) described salutary outcomes when magnesium sulfate therapy was stopped after delivery. That said, these studies are small, and the abbreviated magnesium regimen needs further study before being routinely implemented.

Pharmacology and Toxicology

Using United States Pharmacopeia (USP) standards, magnesium sulfate USP is $MgSO_4 \cdot 7H_2O$, and it contains 8.12 mEq magnesium per 1 g. Parenterally administered magnesium is cleared almost totally by renal excretion, and magnesium intoxication is unusual when the glomerular filtration rate is normal or only slightly reduced. Adequate urine output *usually* correlates with preserved glomerular filtration rates. That said, magnesium excretion is not urine flow dependent, and urinary volume per unit time does not, per se, predict renal function. *Thus, serum creatinine levels must be measured to detect a decreased glomerular filtration rate.*

Eclamptic convulsions are almost always prevented or arrested by plasma magnesium levels maintained at 4 to 7 mEq/L, 4.8 to 8.4 mg/dL, or 2.0 to 3.5 mmol/L. But, one review of magnesium pharmacokinetics showed that most regimens result in much lower serum magnesium levels (Okusanya, 2016). This was especially true if only 1 g/hr was infused (Yefet, 2017). Importantly, the obesity epidemic has affected these observations (Cunningham, 2016). Tudela and colleagues (2013) described our observations from Parkland Hospital with magnesium administration to obese women. More than 60 percent of women whose body mass index (BMI) exceeded 30 kg/m^2 and who were receiving the 2 g/hr dose had subtherapeutic levels at 4 hours. Thus, obese women would require 3 g/hr to maintain effective plasma levels. That said, most currently do not recommend routine magnesium level measurements (American College of Obstetricians and Gynecologists, 2013; Royal College of Obstetricians and Gynaecologists, 2006).

Patellar reflexes disappear when the plasma magnesium level reaches 10 mEq/L—about 12 mg/dL—presumably because of a curariform action. This sign serves to warn of impending magnesium toxicity. When plasma levels rise above 10 mEq/L, breathing becomes weakened. At 12 mEq/L or higher levels, respiratory paralysis and respiratory arrest follow (Somjen, 1966). *Treatment with calcium gluconate or calcium chloride, 1 g intravenously, along with discontinuation of further magnesium sulfate, usually reverses mild-to-moderate respiratory depression.* One of these agents should be readily available whenever magnesium is being infused. Unfortunately, the effects of intravenously administered calcium may be short-lived if there is a steady-state toxic level. For severe respiratory depression and arrest, prompt tracheal intubation and mechanical ventilation are lifesaving. Direct toxic effects on the myocardium from high levels of magnesium are uncommon (McCubbin, 1981; Morisaki, 2000).

Because magnesium is cleared almost exclusively by renal excretion, the dosages described will become excessive if glomerular filtration is substantially decreased. The initial 4-g loading dose of magnesium sulfate can be safely administered regardless of renal function. It is important to administer the standard loading dose and not to reduce it under the mistaken conception that diminished renal function requires it. This is because

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after distribution, a loading dose *achieves* the desired therapeutic level, and the infusion *maintains* the steady-state level. *Thus, only the maintenance infusion rate should be altered with diminished glomerular filtration rate.* Renal function is estimated by measuring plasma creatinine. Whenever plasma creatinine levels are >1.0 mg/mL, serum magnesium levels are determined to guide the infusion rate.

After a 4-g intravenous dose administered over 15 minutes, mean arterial pressure falls slightly, accompanied by a 13-percent rise in cardiac index (Cotton, 1986b). Thus, magnesium lowers systemic vascular resistance and mean arterial pressure. At the same time, cardiac output is increased. These findings are coincidental with transient nausea and flushing, and the cardiovascular effects persist for only 15 minutes despite continued magnesium infusion.

Thurnau and associates (1987) showed that magnesium therapy led to a small but significant rise in the total magnesium concentration in the cerebrospinal fluid. The magnitude of the elevation was directly proportional to the corresponding serum concentration.

Other Effects

Magnesium has anticonvulsant and neuroprotective effects in several animal models. Some proposed mechanisms of action include: (1) reduced presynaptic release of the neurotransmitter glutamate, (2) blockade of glutamatergic *N*-methyl-d-aspartate (NMDA) receptors, (3) potentiation of adenosine action, (4) improved calcium buffering by mitochondria, and (5) blockage of calcium entry via voltage-gated channels (Arango, 2008; Wang, 2012).

In the uterus, relatively high serum magnesium concentrations depress myometrial contractility both in vivo and in vitro. With the suggested regimen, myometrial depression has not been observed, except for a transient decline in activity during and immediately after the initial intravenous loading dose (Leveno, 1998; Szal, 1999; Witlin, 1997). Blood loss at delivery is not increased by standard magnesium treatment (Graham, 2016). However, inhibition of uterine contractility is magnesium dose dependent, and serum levels of at least 8 to 10 mEq/L are necessary to inhibit uterine contractions (Watt-Morse, 1995).

Fetal and Neonatal Effects

Magnesium administered parenterally promptly crosses the placenta to achieve equilibrium in fetal serum and less so in amnionic fluid (Hallak, 1993). Levels in amnionic fluid rise with the duration of maternal infusion (Gortzak-Uzan, 2005). Magnesium sulfate has small but significant effects on the fetal heart rate pattern—specifically beat-to-beat variability (Hallak, 1999). Duffy and associates (2012) reported a lower heart rate baseline that was within the normal range; decreased variability; and fewer prolonged decelerations. They noted no adverse outcomes.

Overall, maternal magnesium therapy appears safe for perinates (Drassinower, 2015). One MFMU Network study of more than 1500 exposed preterm neonates found no association between the need for neonatal resuscitation and cord blood magnesium levels (Johnson, 2012). Still, a few neonatal adverse events are associated with its use. In a Parkland Hospital study of 6654 mostly term, exposed newborns, 6 percent had hypotonia (Abbassi-Ghanavati, 2012). In addition, exposed neonates had lower 1- and 5-minute Apgar scores, a higher intubation rate, and more admissions to the special care nursery. The study showed that neonatal depression occurs only if hypermagnesemia at delivery is severe.

Observational studies suggest a protective effect of magnesium against the development of cerebral palsy in very-low-birthweight newborns (Nelson, 1995; Schendel, 1996). At least five randomized trials have also assessed neuroprotective effects in preterm neonates. These findings are discussed in detail in Chapter 42 (Magnesium Sulfate for Neuroprotection). Nguyen and colleagues (2013) expanded this possibility to include term newborn neuroprotection, but data were insufficient to draw conclusions.

Last, in cases of preterm labor, magnesium has been given for several days for tocolysis (Chap. 42, β-Adrenergic Receptor Agonists). Administration in these instances has been associated with neonatal osteopenia (American College of Obstetricians and Gynecologists, 2016c).

Maternal Safety and Efficacy

The multinational Eclampsia Trial Collaborative Group study (1995) involved 1687 women with eclampsia randomly allocated to one of three different anticonvulsant regimens: magnesium sulfate, diazepam, or phenytoin (Table 40-12). In aggregate, magnesium sulfate therapy was associated with a significantly lower incidence of recurrent seizures (9.7 percent) compared with women given phenytoin (28 percent) or diazepam (17 percent). Importantly, the aggregate maternal death rate of 3.2 percent with magnesium sulfate was significantly lower than that of 5.2 percent for the other two

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TABLE 40-12

Randomized Comparative Trials of Magnesium Sulfate Versus Phenytoin and Diazepam to Prevent Recurrent Eclamptic Convulsions

	Magnesium Sulfate	Phenytoin	Diazepam
Recurrent seizures[a]	60/453 (13%)	126/452 (28%)	—
	22/388 (5.6%)	—	66/389 (17%)
Maternal deaths[b]	10/388 (2.6%)	20/387 (5.2%)	—
	17/453 (3.8%)	—	24/452 (5.3%)

[a]All comparisons $p < 0.01$.

[b]Individual comparisons nonsignificant, combined comparison $p < .05$.

Data from Eclampsia Trial Collaborative Group, 1995.

In their review of more than 9500 treated women, Smith and coworkers (2013) reported the overall rate of absent patellar tendon reflexes to be 1.6 percent; respiratory depression, 1.3 percent; and calcium gluconate administration, 0.2 percent. Only one mother died due to magnesium toxicity. Our experiences are similar. In the more than 60 years of magnesium use at Parkland Hospital, only one woman has died from an overdose (Pritchard, 1984).

MANAGEMENT CONSIDERATIONS

Severe Hypertension Management

Dangerous hypertension can cause cerebrovascular hemorrhage and hypertensive encephalopathy, and it can trigger eclamptic convulsions in women with preeclampsia. Other complications include placental abruption and congestive heart failure induced by elevated hypertensive afterload.

Because of these serious sequelae, the working group for the National High Blood Pressure Education Program (NHBPEP)(2000) and the 2013 Task Force recommend treatment to lower systolic pressures to or below 160 mm Hg and diastolic pressures to or below 110 mm Hg. Martin and associates (2005, 2016) reported provocative observations that highlight the importance of treating systolic hypertension. They described 28 selected women with severe preeclampsia who suffered an associated stroke. Most (93 percent) were hemorrhagic strokes, and all women had systolic pressures >160 mm Hg before suffering their stroke. By contrast, only 20 percent of these same women had diastolic pressures >110 mm Hg.

From other observations, it seems likely that at least half of serious hemorrhagic strokes associated with preeclampsia are in women with chronic hypertension (Cunningham, 2005). Long-standing hypertension results in development of *Charcot-Bouchard aneurysms* in the deep penetrating arteries of the lenticulostriate branch of the middle cerebral arteries. These vessels supply the basal ganglia, putamen, thalamus, and adjacent deep white matter, as well as the pons and deep cerebellum. These unique aneurysmal weakenings predispose these small arteries to rupture during sudden hypertensive episodes.

Several drugs are available to rapidly lower dangerously elevated blood pressure in women with pregnancy-associated hypertension. The three most commonly employed are hydralazine, labetalol, and nifedipine. For years, parenteral hydralazine was the only one of these three available. But when parenteral labetalol was later introduced, it was proven to be equally effective for obstetrical use. Orally administered nifedipine has since also gained popularity. All three of these are recommended as first-line agents by the American College of Obstetricians and Gynecologists (2017a).

Hydralazine

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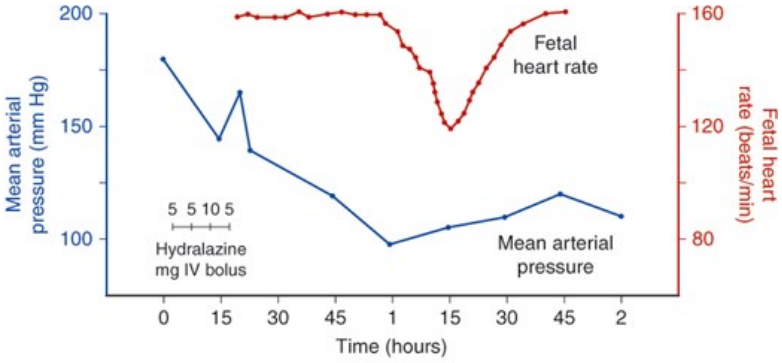
This is probably still the most commonly used antihypertensive agent in the United States for treatment of women with severe gestational hypertension. Hydralazine is administered intravenously with a 5- to 10-mg initial dose, and this is followed by 10-mg doses at 15- to 20-minute intervals until a satisfactory response is achieved. Although we will administer a third dose, the American College of Obstetricians and Gynecologists (2017a) recommends labetalol therapy if severe hypertension persists after the second dose. Antepartum or intrapartum, the target response is a decline in systolic pressure to <160 mm Hg and diastolic blood pressure to 90 to 110 mm Hg. Lower diastolic pressures risk compromised placental perfusion. Hydralazine has proven remarkably effective to prevent cerebral hemorrhage. Its onset of action can be as rapid as 10 minutes. Although repeated administration every 15 to 20 minutes may theoretically lead to undesirable hypotension, this has not been our experience when given in these 5- to 10-mg increments.

At Parkland Hospital, between 5 and 10 percent of all women with intrapartum hypertensive disorders are given a parenteral antihypertensive agent. Antepartum, we usually give hydralazine as described. We do not limit the total dose, and seldom is a second antihypertensive agent needed. We estimate that nearly 6000 women have been so treated at our facility during the past 50 years. Although less popular in Europe, hydralazine is used in some centers according to the Royal College of Obstetricians and Gynaecologists (2006).

For higher blood pressures, there is a tendency to give a larger initial dose of hydralazine. But, this must be avoided. The response to even 5- to 10-mg doses cannot be predicted by hypertension severity. Thus, our protocol is to always administer 5 mg as the initial dose. An adverse response to exceeding this initial dose is shown in Figure 40-20. This woman had chronic hypertension complicated by severe superimposed preeclampsia, and hydralazine was injected more frequently than recommended. Her blood pressure in less than 1 hour dropped from 240–270/130–150 mm Hg to 110/80 mm Hg. Fetal heart rate decelerations characteristic of uteroplacental insufficiency became evident. Decelerations persisted until her blood pressure was increased with rapid crystalloid infusion. In some cases, this fetal response to diminished uterine perfusion may be confused with placental abruption and may result in unnecessary and potentially dangerous emergency cesarean delivery.

FIGURE 40-20

Hydralazine was given at 5-minute intervals instead of 15-minute intervals. The mean arterial pressure dropped from 180 to 90 mm Hg within 1 hour and was associated with fetal bradycardia. Rapid crystalloid infusion raised the mean pressure to 115 mm Hg, and the fetus recovered.



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Labetalol

This effective intravenous antihypertensive agent is an α- and nonselective β-blocker. Some prefer its use over hydralazine because of fewer side effects. At Parkland Hospital, we give 10 mg intravenously initially. If the blood pressure has not decreased to the desirable level in 10 minutes, then 20 mg is given. The next 10-minute incremental dose is 40 mg and is followed by another 40 mg if needed. If a salutary response is not achieved, then an 80-mg dose is given. Sibai (2003) recommends 20 to 40 mg every 10 to 15 minutes as needed and a maximum dose of 220 mg per treatment cycle. The American College of Obstetricians and Gynecologists (2017a) recommends starting with a 20-mg intravenous bolus. If not effective within 10 minutes, this is followed by 40 mg, then 80 mg every 10 minutes. If hypertension persists, hydralazine is then given.

Comparative studies of hydralazine versus labetalol show equivalent results (Umans, 2015). In one trial, labetalol lowered blood pressure more rapidly, and associated tachycardia was minimal. But, hydralazine lowered mean arterial pressures to safe levels more effectively (Mabie, 1987). In

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another trial, maternal and neonatal outcomes were similar (Vigil-De Gracia, 2007). Hydralazine causes significantly more maternal tachycardia and palpitations, whereas labetalol more frequently leads to maternal hypotension and bradycardia. Both drugs have been associated with a reduced frequency of fetal heart rate accelerations (Cahill, 2013). Labetalol is not given to asthmatic women.

Nifedipine

This orally administered calcium-channel blocking agent has become popular because of its efficacy to control acute pregnancy-related hypertension. The American College of Obstetricians and Gynecologists (2017a), the NHBPEP Working Group (2000), and the Royal College of Obstetricians and Gynaecologists (2006) recommend a 10-mg initial immediate-release oral dose to be followed in 20 to 30 minutes with 10 to 20 mg if necessary. If not satisfactory, this is followed by labetalol. *Nifedipine given sublingually is no longer recommended.* This route is associated with dangerously rapid and extensive effects. Randomized trials that compared nifedipine with labetalol found neither drug definitively superior, but nifedipine lowered blood pressure more quickly (Scardo, 1999; Shekhar, 2016; Vermillion, 1999). Finally, nifedipine does not potentiate magnesium-related effects (Magee, 2015).

Other Antihypertensive Agents

A few other generally available antihypertensive agents have been tested in clinical trials but are not widely used (Umans, 2015). These include verapamil, nitroglycerin, nitroprusside, ketanserin, nicardipine, and nimodipine (Belfort, 1990, 2003; Bolte, 2001; Cornette, 2016). There are also experimental antihypertensive drugs that may become useful for preeclampsia treatment (Lam, 2013).

Diuretics

Potent loop diuretics can further compromise placental perfusion. Immediate effects include redistribution of the intravascular volume, which most often is already reduced in severe preeclampsia (Blood Volume). Therefore, before delivery, diuretics are not used to lower blood pressure (Zeeman, 2009; Zondervan, 1988). We use *antepartum* furosemide or similar drugs solely to treat pulmonary edema.

Fluid Therapy

Lactated Ringer solution is administered routinely at a rate between 60 and 125 mL per hour, unless fluid loss is unusual from vomiting, diarrhea, or diaphoresis, or, more likely, excessive blood loss with delivery. Oliguria is common with severe preeclampsia. Thus, coupled with the knowledge that maternal blood volume is likely constricted compared with that of normal pregnancy, it is tempting to administer intravenous fluids more vigorously. But controlled, conservative fluid administration is preferred for the typical woman with severe preeclampsia who already has excessive extracellular fluid that is inappropriately distributed between intravascular and extravascular spaces. Infusion of large fluid volumes enhances the maldistribution and thereby appreciably elevates the risk of pulmonary and cerebral edema (Dennis, 2012a; Sciscione, 2003; Zinaman, 1985). Thus, for preeclamptic women with anuria, small incremental boluses can be given to maintain urine output above 30 mL per hour. Diminished intravascular volume from hemorrhage or fluid loss from vomiting or fever can similarly be replaced by gradual incremental boluses. For labor analgesia with neuraxial analgesia, crystalloid solutions are infused slowly in graded amounts (Chap. 25, Safety).

Pulmonary Edema

Women with severe preeclampsia who develop pulmonary edema most often do so postpartum (Cunningham, 1986, 2012; Zinaman, 1985). With suspected pulmonary edema in the eclamptic woman, aspiration of gastric contents, which may be the result of convulsions, anesthesia, or oversedation, should be excluded. There are three common causes of pulmonary edema in women with severe preeclampsia syndrome—pulmonary capillary permeability edema, cardiogenic edema, or a combination of the two.

Some women with severe preeclampsia—especially if given vigorous fluid replacement—will have mild pulmonary congestion secondary to permeability edema. This is caused by normal pregnancy changes magnified by the preeclampsia syndrome. Importantly, plasma oncotic pressure drops appreciably in normal term pregnancy because of decreased serum albumin concentration, and oncotic pressure falls even more with preeclampsia (Zinaman, 1985). Moreover, both increased extravascular fluid oncotic pressure and increased capillary permeability are found in women with preeclampsia (Brown, 1989; Øian, 1986).

Invasive Hemodynamic Monitoring

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Knowledge concerning cardiovascular and hemodynamic pathophysiological alterations associated with severe preeclampsia-eclampsia has accrued from studies done using invasive monitoring and a flow-directed pulmonary artery catheter (see Fig. 40-5). Two conditions frequently cited as indications are preeclampsia associated with oliguria and that associated with pulmonary edema (Clark, 2010). Somewhat ironically, it is usually vigorous treatment of the former that results in most cases of the latter. The Task Force (2013) recommends against routine invasive monitoring. Such monitoring is best reserved for severely preeclamptic women with accompanying cardiac disease, renal disease, or both or with refractory hypertension, oliguria, and pulmonary edema.

Plasma Volume Expansion

Because the preeclampsia syndrome is associated with hemoconcentration, some have infused various fluids, starch polymers, albumin concentrates, or combinations thereof to expand blood volume (Ganzevoort, 2004). Older observational studies describe serious complications—especially pulmonary edema—with volume expansion (Benedetti, 1985; López-Llera, 1982; Sibai, 1987b).

The Amsterdam randomized study reported by Ganzevoort and coworkers (2005a,b) was a well-designed investigation done to evaluate volume expansion. A total of 216 women with severe preeclampsia were enrolled between 24 and 34 weeks' gestation. The study included women whose preeclampsia was complicated by HELLP syndrome, eclampsia, or fetal-growth restriction. In the group randomly assigned to volume expansion, each woman was given 250 mL of 6-percent hydroxyethyl starch infused over 4 hours twice daily. Their outcomes were compared with a control group, and none of these outcomes were significantly different (Table 40-13). Importantly, serious maternal morbidity and a substantive perinatal mortality rate accompanied their "expectant" management (see Table 40-9).

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TABLE 40-13

Maternal and Perinatal Outcomes after Enrollment in a Randomized Trial of Plasma Volume Expansion versus Saline Infusion in 216 Women with Severe Preeclampsia between 24 and 34 Weeks

Outcomes	Control Group[a] (n = 105)	Treatment Group[a] (n = 111)
Maternal Outcomes (%)		
Eclampsia	1.9	1.8
HELLP	19.0	17.0
Pulmonary edema	2.9	4.5
Placental abruption	3.8	1.0
Perinatal Outcomes		
Fetal deaths (%)	7	12
Prolongation of pregnancy (mean)	11.6 d	6.7 d
EGA at death (mean)	26.7 wk	26.3 wk
Birthweight (mean)	625 g	640 g
Live births (%)	93	88
Prolongation of pregnancy (mean)	10.5 d	7.4 d
EGA at delivery (mean)	31.6 wk	31.4 wk
RDS (%)	30	35
Neonatal death (%)	7.6	8.1
Perinatal mortality rate (n per 1000)	142/1000	207/1000

[a]All comparisons $p > 0.05$.

EGA = estimated gestational age; HELLP = hemolysis, elevated liver enzyme levels, low platelet count; RDS = respiratory distress syndrome.

Data from Ganzevoort, 2005a, b.

Neuroprophylaxis—Prevention of Seizures

Several randomized trials have tested the efficacy of seizure prophylaxis for women with gestational hypertension, with or without proteinuria. In most of these, magnesium sulfate was compared with another anticonvulsant or with a placebo. *In all studies, magnesium sulfate was reported to be superior to the comparator agent to prevent eclampsia.* Four of the larger studies are summarized in Table 40-14. In the study from Parkland Hospital, magnesium sulfate therapy was superior to phenytoin to prevent eclamptic seizures in women with gestational hypertension or preeclampsia (Lucas,

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1995). In another, magnesium sulfate and nimodipine—a calcium-channel blocker with specific cerebral vasodilator activity—were compared in 1650 women with severe preeclampsia (Belfort, 2003). The rate of eclampsia was more than threefold higher for women allocated to the nimodipine group—2.6 versus 0.8 percent.

TABLE 40-14

Randomized Comparative Trials of Prophylaxis with Magnesium Sulfate and Placebo or Another Anticonvulsant in Women with Gestational Hypertension

	No. with Seizures/Total No. Treated (%)		
Study/Inclusions	**Magnesium Sulfate**	**Control**	**Comparison[a]**
Lucas et al (1995)		Phenytoin	
Gestational hypertension[b]	0/1049 (0)	10/1089 (0.9)	$p < 0.001$
Coetzee et al (1998)		Placebo	
Severe preeclampsia	1/345 (0.3)	11/340 (3.2)	RR = 0.09 (0.1–0.69)
Magpie Trial (2002)[c]		Placebo	
Severe preeclampsia	40/5055 (0.8)	96/5055 (1.9)	RR = 0.42 (0.26–0.60)
Belfort et al (2003)		Nimodipine	
Severe preeclampsia	7/831 (0.8)	21/819 (2.6)	RR = 0.33 (0.14–0.77)

[a]All comparisons significant $p < 0.05$.

[b]Included women with and without proteinuria and those with all severities of preeclampsia.

[c]Magpie Trial Collaboration Group, 2002.

RR = relative risk.

The largest comparative study was *Magnesium Sulfate for Prevention of Eclampsia* reported by the Magpie Trial Collaboration Group (2002). More than 10,000 women with severe preeclampsia from 33 countries were randomly allocated to treatment with magnesium sulfate or placebo. Women given magnesium had a 58-percent significantly lower risk of eclampsia than those given placebo. In follow-up data of infants born to these mothers given magnesium sulfate, child behavior at approximately 18 months did not differ in those exposed compared with those not exposed to magnesium sulfate (Smyth, 2009).

Who Should Be Given Magnesium Sulfate?

Magnesium will prevent proportionately more seizures in women with correspondingly worse disease. However, severity is difficult to quantify, and thus deciding which individual woman might benefit most from neuroprophylaxis is difficult. *The 2013 Task Force recommends that women with either eclampsia or severe preeclampsia should be given magnesium sulfate prophylaxis.* Again, criteria that establish "severity" are not totally uniform (see Table 40-2). At the same time, however, the 2013 Task Force suggests that women with "mild" preeclampsia do not need magnesium

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sulfate neuroprophylaxis. The conundrum is whether or not to give neuroprophylaxis to any of these women with "nonsevere" gestational hypertension or preeclampsia (Alexander, 2006).

In most other countries, and principally following dissemination of the Magpie Trial Collaboration Group (2002) study results, magnesium sulfate is now recommended for women with severe preeclampsia. In some, however, debate continues concerning whether therapy should be reserved for women who have an eclamptic seizure. We believe that eclamptic seizures are dangerous (Brain and Renal Sequelae). Maternal mortality rates of up to 5 percent have been reported even in recent studies. Moreover, perinatal mortality rates are substantially increased (Abd El Aal, 2012; Knight, 2007; Ndaboine, 2012; Schutte, 2008; von Dadelszen, 2012). Finally, the possibility of adverse long-term neuropsychological and vision-related sequelae of eclampsia have raised additional concerns that eclamptic seizures are not "benign."

Selective versus Universal Prophylaxis

Because of the foregoing, there is uncertainty about which women with *nonsevere* gestational hypertension should be given magnesium sulfate neuroprophylaxis. An opportunity to address these questions was afforded by a change in our prophylaxis protocol at Parkland Hospital. Before this time, the risk of eclampsia without magnesium prophylaxis was approximately 1 in 100 for women with *mild preeclampsia* (Lucas, 1995). Up until 2000, all women with gestational hypertension were given magnesium prophylaxis intramuscularly. After 2000, we instituted a standardized protocol for intravenously administered magnesium sulfate (Alexander, 2006). At the same time, we also changed our practice of universal seizure prophylaxis for all women with gestational hypertension to one of selective prophylaxis given only to women who met our criteria for severe gestational hypertension. These criteria, shown in Table 40-15, included women with ≥2+ proteinuria measured by dipstick in a catheterized urine specimen.

TABLE 40-15

Selective versus Universal Magnesium Sulfate Prophylaxis: Parkland Hospital Criteria to Define Severe Gestational Hypertension or Preeclampsia

In a woman with new-onset proteinuric hypertension, at least one of the following criteria is required:
Systolic BP ≥160 or diastolic BP ≥110 mm Hg
Proteinuria ≥2+ by dipstick in a catheterized urine specimen
Serum creatinine >1.1 mg/dL
Platelet count <100,000/μL
Aspartate aminotransferase (AST) elevated two times above upper limit of normal range
Persistent headache or scotomata
Persistent midepigastric or right-upper quadrant pain

BP = blood pressure.

Criteria based on those from National High Blood Pressure Education Program Working Group, 2000; American College of Obstetricians and Gynecologists, 2012; cited by Alexander, 2006.

Following this protocol change, 60 percent of 6518 women with gestational hypertension during a 4½-year period were given magnesium sulfate neuroprophylaxis. The remaining 40 percent with nonsevere hypertension were not treated, and of these, 27 women developed eclamptic seizures—1 in 92. The seizure rate was only 1 in 358 for 3935 women with criteria for severe disease who were given magnesium sulfate, and thus these cases were treatment failures.

To assess morbidity, outcomes in 87 eclamptic women were compared with outcomes in all 6431 noneclamptic severely hypertensive women

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(Alexander, 2006). Although most maternal outcomes were similar, almost a fourth of women with eclampsia who underwent emergent cesarean delivery required general anesthesia. This is a great concern because eclamptic women have laryngotracheal edema and are at a higher risk for failed intubation, gastric acid aspiration, and death. Neonatal outcomes were also a concern because the composite morbidity was increased tenfold in eclamptic compared with noneclamptic women—12 versus 1 percent, respectively. These outcomes included cord artery pH <7.0; 5-minute Apgar score <4; or unanticipated admission of a term newborn to an intensive care nursery.

Thus, if one uses the Parkland criteria for nonsevere gestational hypertension, approximately 1 of 100 such women who are not given magnesium sulfate prophylaxis can be expected to have an eclamptic seizure. A fourth of these women likely will require emergent cesarean delivery with attendant maternal and perinatal morbidity and mortality from general anesthesia. From this, the major question regarding management of nonsevere gestational hypertension remains whether it is acceptable to avoid unnecessary treatment of 99 women to risk eclampsia in one? The answer appears to be yes as suggested by the 2013 Task Force. At Parkland Hospital, we only give magnesium neuroprophylaxis to women with severe criteria.

Analgesia and Anesthesia

During the past 20 years, the use of conduction analgesia for women with preeclampsia syndrome has proven ideal. Initial problems with this method included hypotension and diminished uterine perfusion caused by sympathetic blockade in preeclamptic women, with already attenuated hypervolemia. But pulmonary edema was mitigated by techniques that used slow induction of epidural analgesia with dilute solutions of anesthetic agents. This countered the need for rapid infusion of large volumes of crystalloid or colloid to correct maternal hypotension from neural blockade (Hogg, 1999; Wallace, 1995). These techniques are described in detail in Chapter 25 (Safety). Importantly, epidural blockade avoids general anesthesia, in which the stimulation of tracheal intubation may cause sudden severe hypertension. Such blood pressure spikes, in turn, can cause pulmonary edema, cerebral edema, or intracranial hemorrhage. Finally, tracheal intubation may be particularly difficult and thus hazardous in women with airway edema due to preeclampsia (American College of Obstetricians and Gynecologists, 2017b).

At least three randomized studies have been performed to compare these methods of analgesia and anesthesia. Wallace and colleagues (1995) studied 80 women at Parkland Hospital with severe preeclampsia who were to undergo cesarean delivery. They had not been given labor epidural analgesia and were randomly assigned to receive general anesthesia, epidural analgesia, or combined spinal-epidural analgesia. Their average preoperative blood pressures approximated 170/110 mm Hg, and all had proteinuria. Maternal and perinatal outcomes in each group were similar. Maternal hypotension resulting from regional analgesia was managed with judicious intravenous fluid administration. In women undergoing general anesthesia, maternal blood pressure was managed to avoid severe hypertension. There were no serious maternal or fetal complications attributable to any of the three anesthetic methods. It was concluded that all three are acceptable for use in women with pregnancies complicated by severe preeclampsia if steps are taken to ensure a careful approach to the selected method.

Another randomized study included 70 women with severe preeclampsia receiving spinal analgesia versus general anesthesia for cesarean delivery (Dyer, 2003). Their maternal and fetal outcomes were equivalent. In a third study, 116 women with severe preeclampsia received either epidural or patient-controlled intravenous meperidine analgesia during labor (Head, 2002). More women—9 percent—from the group assigned to epidural analgesia required ephedrine for hypotension. As expected, pain relief was superior in the epidural group. Maternal and neonatal complications were similar between groups, and one woman in each group developed pulmonary edema. Importantly, epidural analgesia is not considered *treatment* of preeclampsia (Lucas, 2001; Ray, 2017).

Judicious fluid administration is essential in severely preeclamptic women who receive regional analgesia. Vigorous crystalloid infusion with epidural blockade in women with severe preeclampsia elevates pulmonary capillary wedge pressures (Newsome, 1986). Aggressive volume replacement in preeclamptic women raises their risk for pulmonary edema, especially in the first 72 hours postpartum (Clark, 1985; Cotton, 1986a). Finally, most cases of pharyngolaryngeal edema are related to aggressive volume therapy (Heller, 1983).

Blood Loss at Delivery

Hemoconcentration or lack of normal pregnancy-induced hypervolemia is an almost predictable feature of severe preeclampsia-eclampsia (see Fig. 40-7) (Zeeman, 2009). *These women, who consequently lack normal pregnancy hypervolemia, are much less tolerant of even normal blood loss than are normotensive pregnant women.* Importantly, an appreciable fall in blood pressure soon after delivery most often means excessive blood loss and not sudden resolution of vasospasm and endothelial damage. When oliguria follows delivery, the hematocrit should be evaluated frequently to help

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detect excessive blood loss. If identified, hemorrhage should be treated appropriately by crystalloid and blood transfusion.

Persistent Severe Postpartum Hypertension

Although severe postpartum hypertension usually follows labor and delivery complicated by hypertension, 8 percent of women develop de novo hypertension postpartum (Goel, 2015). In either case, if difficulty arises in controlling severe hypertension or if intravenous hydralazine or labetalol are being used repeatedly, then oral regimens can be given. Examples include labetalol or another β-blocker, or nifedipine or another calcium-channel blocker (Sharma, 2017). Women so treated are less likely to require readmission (Hirshberg, 2016). Persistent or refractory hypertension is likely aggravated by mobilization of pathological interstitial fluid and redistribution into the intravenous compartment, underlying chronic hypertension, or usually both (Sibai, 2012; Tan, 2002). Chronic, but not sporadic, administration of some nonsteroidal antiinflammatory drugs, namely ibuprofen, may aggravate postpartum hypertension in those with preeclampsia (Vigil-De Gracia, 2017; Viteri, 2017). In women with chronic hypertension and left-ventricular hypertrophy, severe postpartum hypertension can cause pulmonary edema from cardiac failure (Cunningham, 1986, 2012; Sibai, 1987a).

Furosemide

Because persistence of severe hypertension corresponds to the onset and length of diuresis and extracellular fluid mobilization, it seems logical that furosemide-augmented diuresis might serve to hasten blood pressure control. One randomized trial included 264 postpartum preeclamptic women who, after onset of spontaneous diuresis, were assigned to 20-mg oral furosemide given daily or to no therapy (Ascarelli, 2005). Women with mild disease had similar blood pressure control regardless of whether they received treatment or placebo. However, after 2 days, women with severe preeclampsia who were treated, compared with those receiving placebo, had a lower mean systolic blood pressure—142 versus 153 mm Hg. They also less frequently required supplemental antihypertensive therapy during the remainder of hospitalization—14 versus 26 percent, respectively. In a recent randomized study, Veena and colleagues (2017) treated severe postpartum eclampsia with nifedipine plus furosemide or nifedipine alone. They reported that this prophylactic therapy significantly lowered the need for an additional antihypertensive—26 versus 8 percent, respectively.

We use a simple method to estimate excessive extracellular/interstitial fluid. The *postpartum weight* is compared with the most recent *prenatal weight*, either from the last clinic visit or on admission for delivery. Typically, soon after delivery, maternal weight should be reduced by at least 10 to 15 pounds depending on newborn and placental weight, amnionic fluid volume, and blood loss. Because of various interventions, especially intravenous crystalloid infusions given with labor epidural analgesia or during operative vaginal or cesarean delivery, women with severe preeclampsia often have an immediate postpartum weight *in excess of their last prenatal weight*. If this weight increase is associated with severe persistent postpartum hypertension, then diuresis with intravenous furosemide is usually helpful in controlling blood pressure.

Plasma Exchange

Occasionally, women have an atypical syndrome in which severe preeclampsia-eclampsia persists despite delivery. Martin and colleagues (1995) described 18 such women whom they encountered during a 10-year period. They advocate single or multiple plasma exchange for these women. In some cases, 3 L of plasma was exchanged three times—a 36- to 45-donor unit exposure for each patient—before a response was forthcoming. Others have described plasma exchange performed in postpartum women with HELLP syndrome (Förster, 2002; Obeidat, 2002). In all of these cases, however, the distinction between HELLP syndrome and thrombotic thrombocytopenic purpura or hemolytic uremic syndrome was not clear (Tsai, 2016).

In our experiences with more than 50,000 women with gestational hypertension among nearly 450,000 pregnancies cared for at Parkland Hospital through 2017, we have encountered very few women with persistent postpartum hypertension, thrombocytopenia, and renal dysfunction who were diagnosed as having a thrombotic microangiopathy (Dashe, 1998). These latter syndromes complicating pregnancy were reviewed by Martin (2008) and George (2013) and their colleagues, who conclude that a rapid diagnostic test for ADAMTS-13 enzyme activity might be helpful to differentiate most of these syndromes.

Reversible Cerebral Vasoconstriction Syndrome

This is another cause of persistent hypertension, “thunderclap” headaches, seizures, and central nervous system findings. It is a form of postpartum angiopathy. *Reversible cerebral vasoconstriction syndrome* is characterized by diffuse segmental constriction of cerebral arteries and may be associated with ischemic and hemorrhagic strokes. This syndrome has several inciting causes that include pregnancy, and particularly preeclampsia (Ducros, 2012). It is more common in women, and in some cases, vasoconstriction may be so severe as to cause cerebral ischemia and infarction. The

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appropriate management is not known at this time (Edlow, 2013).

LONG-TERM CONSEQUENCES

Future Pregnancies

Defective remodeling of the spiral arteries in some placentas is posited as a cause of at least one preeclampsia phenotype. Specifically, lack of deep placentation is linked with preeclampsia, placental abruption, fetal-growth restriction, and preterm birth (Wikström, 2011). With this type of "overlap syndrome," hypertensive disorders may serve as markers for subsequent preterm labor and fetal-growth restriction. For example, even in subsequent nonhypertensive pregnancies, women who had preterm preeclampsia are at higher risk for preterm birth and growth-restricted neonates (Bramham, 2011; Connealy, 2014; Palatnik, 2016).

In addition, women who have had either gestational hypertension or preeclampsia risk developing hypertension in future pregnancies (Lykke, 2009b). Generally, the earlier preeclampsia is diagnosed during the index pregnancy, the greater the likelihood of recurrence. And, the recurrence risk for preeclampsia is elevated further in women with the metabolic syndrome (Stekkinger, 2015). Sibai and colleagues (1986, 1991) found that nulliparas diagnosed with preeclampsia before 30 weeks had a recurrence risk as high as 40 percent during a subsequent pregnancy. In a prospective study of 500 women previously delivered for preeclampsia at 37 weeks, the recurrence rate in a subsequent gestation was 23 percent (Bramham, 2011).

As perhaps expected, women with HELLP syndrome have a substantive risk for recurrence in subsequent pregnancies. In two studies, the risk ranged from 5 to 26 percent, but the true recurrence risk likely lies between these two extremes (Habli, 2009; Sibai, 1995). Even if HELLP syndrome does not recur with subsequent pregnancies, again incidences of preterm delivery, fetal-growth restriction, placental abruption, and cesarean delivery are increased (Habli, 2009; Hnat, 2002).

Long-Term Morbidity and Mortality

Evidence has accrued that the preeclampsia syndrome is a marker for subsequent long-term cardiovascular and related morbidity and mortality (Table 40-16). Thus, women with hypertension identified during pregnancy should be evaluated during the first several months postpartum. The working group of the NHBPEP (2000) concluded that hypertension attributable to pregnancy should resolve within 12 weeks of delivery. Hypertension persisting beyond this time is considered chronic (Chap. 50, Definition and Classification). The Magpie Trial Follow-Up Collaborative Group (2007) reported that 20 percent of 3375 preeclamptic women seen at a median of 26 months postpartum had hypertension. Importantly, even if hypertension does not persist in the short term, convincing evidence suggests a higher risk for long-term cardiovascular morbidity.

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TABLE 40-16

Some Long-Term Consequences in Women with Preeclampsia Syndrome

Cardiovascular
Chronic hypertension
Ischemic heart disease
Atherosclerosis
Coronary artery calcification
Cardiomyopathy
Thromboembolism
Neurovascular
Stroke
Retinal detachment
Diabetic retinopathy
Metabolic
Type 2 diabetes
Metabolic syndrome
Dyslipidemia
Obesity
Renal
Glomerular dysfunction
Proteinuria
Central nervous system
White-matter lesions
Cognitive dysfunction
Retinopathy

Cardiovascular Morbidity

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Any hypertension during pregnancy is a risk marker for morbidity and mortality in later life (American College of Obstetricians and Gynecologists, 2013; Bellamy, 2007). In a case-control study from Iceland, Arnadottir and associates (2005) reported the prevalences of *ischemic heart disease*—24 versus 15 percent, and *stroke*—9.5 versus 6.5 percent, were significantly increased in women who had gestational hypertension compared with normotensive controls. In a Swedish population study of more than 400,000 women, those with recurrent preeclampsia have systolic dysfunction and a greater incidence of ischemic heart disease (Valensise, 2016). Diastolic dysfunction is also more common (Bokslag, 2017). Preeclampsia is also a risk for coronary artery calcification and idiopathic cardiomyopathy (Behrens, 2016; White, 2016).

Lykke and associates (2009a) cited findings from a Danish registry of more than 780,000 nulliparas. After a mean follow-up of almost 15 years, the incidence of *chronic hypertension* was fivefold higher in those who had gestational hypertension, 3.5-fold greater after mild preeclampsia, and sixfold higher after severe preeclampsia. After two hypertensive pregnancies, this incidence rose sixfold. Moreover, these women with pregnancy-associated hypertension are at increased risk for *type 2 diabetes* (Rice, 2016). And, preeclampsia is a risk factor for later diabetic retinopathy and retinal detachment (Auger, 2017; Beharier, 2016).

As emphasized by several investigators, other cofactors or comorbidities are related to acquisition of these long-term adverse outcomes (Gastrich, 2012; Harskamp, 2007; Hermes, 2012; Spaan, 2012b). These include the metabolic syndrome, diabetes, obesity, dyslipidemia, and atherosclerosis (Kajantie, 2017; Orabona, 2016; Stekkinger, 2015).

Individuals who are born preterm have greater ventricular mass later in life (Lewandowski, 2013). And, women who have preeclampsia and who develop chronic hypertension later in life have an increased ventricular mass index before they become hypertensive (Ghossein-Doha, 2013). Finally, in at least some of these women, hypertensive cardiovascular pathologies appear to have begun near the time of *their own* births. A similar phenomenon is associated with preterm birth and with fetal-growth disorders.

Renal Sequelae

Preeclampsia is also a marker for subsequent renal disease. Almost 15 percent of previously preeclamptic women have renal dysfunction (Lopes van Balen, 2017). In a 40-year study of Norwegian birth and end-stage renal disease linked registries, although the absolute risk of renal failure was small, preeclampsia was associated with a fourfold greater risk (Vikse, 2008). Women with recurrent preeclampsia had an even higher risk. These data need to be considered in light of the findings that 15 to 20 percent of women with preeclampsia who undergo renal biopsy have evidence of chronic renal disease (Chesley, 1978). In another long-term study, Spaan and coworkers (2009) compared formerly preeclamptic women with a cohort of women who were normotensive at delivery. At 20 years following delivery, preeclamptic women were significantly more likely to be chronically hypertensive—55 versus 7 percent—compared with control women. They also had higher peripheral vascular and renovascular resistance and decreased renal blood flow. These data do not permit conclusions as to cause versus effect.

Central Nervous System Sequelae

Until recently, eclamptic seizures were believed to have no significant long-term sequelae. However, this may not be the case (Theilen, 2016). Recall that almost all eclamptic women have multifocal areas of perivascular edema, and approximately a fourth also have areas of cerebral infarction (Zeeman, 2004a).

In several long-term follow-up studies in women with severe preeclampsia and eclampsia, brain white-matter lesions that followed eclamptic convulsions persist (Aukes, 2007, 2009, 2012). Specifically, when studied with MR imaging at a mean of 7 years, 40 percent of formerly eclamptic women had more numerous and larger aggregate white matter lesions compared with 17 percent of normotensive control women. These investigators later also observed these white-matter lesions in preeclamptic women without convulsions (Aukes, 2012). And, Siepmann and associates (2017) documented temporal lobe white matter changes and reduced cortical volume in previously preeclamptic women. In studies designed to assess clinical relevance, formerly eclamptic women had subjectively impaired cognitive functioning (Postma, 2014). Wiegman and associates (2012) reported that formerly eclamptic women at approximately 10 years had lower vision-related quality of life compared with control subjects. This likely coincides with an elevated risk for retinopathy described by Auger and colleagues (2017). Because no baseline studies were done before these women suffered from preeclampsia or eclampsia, the investigators appropriately concluded that a cause versus an effect of these white-matter lesions remains unknown.

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