Hypertensive disorders of pregnancy are one of the most serious complications in pregnancy because they cause serious maternal and perinatal morbidity and mortality. Although numerous hypertensive patients have relatively good outcome, difficulty in differentiating among various hypertensive conditions, inability to predict which patients are at highest risk, and variability in the progression of preeclampsia make these disorders the greatest challenge of clinical medicine in obstetrics.

CLASSIFICATION

Various systems have been used to classify hypertensive disorders of pregnancy. Some terms, such as pregnancy-induced hypertension, have misleading connotations about the underlying mechanism. Misleading terms reflect the lack of clear understanding about the etiology and lack of a gold standard diagnostic test. The current classification was developed by the National Institutes of Health working group on hypertension in pregnancy. This classification proposes that hypertensive disorders of pregnancy be divided into four categories: preeclampsia-eclampsia, gestational hypertension, chronic hypertension, and preeclampsia superimposed on chronic hypertension.

Preeclampsia-Eclampsia

Preeclampsia is new-onset hypertension with proteinuria with or without edema. Edema alone with hypertension is unreliable for diagnosis of preeclampsia because significant edema occurs in normal pregnancy, and it is difficult to distinguish physiologic change from pathologic edema. Edema that occurs in nondependent sites, rapidly increasing edema (as evidenced by rapid weight gain of at least 2.25 kg or 5 lb per week), or persisting facial edema after the patient has been upright for several hours should be suspected as pathologic edema. Hypertension is defined as blood pressure greater than 140/90 mm Hg or mean arterial pressure greater than 105 mm Hg. Proteinuria is defined as protein excretion of 30 mg/dL in a random specimen (equal to 1+ on urine strips) or 300 mg in a 24-hour urine specimen. Eclampsia is the development of convulsions or coma or both in the clinical setting of preeclampsia.

Gestational Hypertension

Gestational hypertension is hypertension occurring after the 20th week of pregnancy or during the first 24 hours postpartum without evidence of proteinuria or other signs of preeclampsia and in the absence of evidence of preexisting hypertension.

Chronic Hypertension

Chronic hypertension is hypertension diagnosed before pregnancy or before the 20th week of pregnancy. Hypertension is defined as blood pressure greater than 140/90 mm Hg. This definition may overlook isolated systolic or diastolic hypertension. Some investigators have suggested use of mean arterial pressure greater than 105 mm Hg as the alternative diagnostic criterion. Mean arterial pressure is calculated as diastolic pressure plus one-third pulse pressure (pulse pressure is systolic pressure minus diastolic pressure). Hypertension diagnosed any time during pregnancy but persisting beyond the 42nd postpartum day is also classified as chronic hypertension.

Superimposed Preeclampsia

Superimposed preeclampsia is either aggravation of hypertension or onset or increase in degree of proteinuria in a patient with a chronic hypertensive disorder. Aggravation of hypertension is an increase in systolic pressure by 30 mm Hg or diastolic pressure by 15 mm Hg.
Comment on Classification

Increases of 30 mm Hg in systolic blood pressure and of 15 mm Hg in diastolic blood pressure have been shown to be unreliable criteria for diagnosis of preeclampsia. Most patients with an increase of this magnitude do not have a hypertensive disorder. One of the difficulties of diagnosing hypertension before the 20th week of gestation is that a patient’s blood pressure is generally lower in the first half of pregnancy compared with the nonpregnant state. The lowering of blood pressure is a result of the vasorelaxant effect of gestation, which masks hypertension in some patients before the 20th week of pregnancy. Patients with chronic hypertension have been shown to have a greater decline in their blood pressure than normal patients. Diagnosis of chronic hypertension as persisting after the 42nd postpartum day is useful only for classifying patients retrospectively (e.g., for grouping patients in a study), but is not useful for clinicians in managing the index pregnancy.

PREECLAMPSIA–ECLAMPSIA

Pathophysiology

Uteroplacental ischemia is a fundamental abnormality recognized in preeclampsia–eclampsia. The diagnosis of uteroplacental ischemia is based on histopathologic examination of the placenta, revealing ischemic lesions; study of the uterine vascular bed, revealing vascular lesions known as acute atherosclerosis; restriction of fetal growth secondary to reduced uteroplacental blood flow; and radionuclide studies of uteroplacental perfusion, showing reduced clearance of radionuclide. Understanding the pathogenic mechanism requires understanding uterine vascular modeling in implantation and development of the placenta and understanding the mechanisms of regulation of blood flow in the maternal uteroplacental vasculature.

UTERINE VASCULAR MODELING

Terminal uterine vessels are known as spiral arteries. In the process of gestational development, under the influence of sex steroids, these vessels grow in length and to some degree in diameter. Trophoblastic invasion of these vessels occurs in the process of implantation and development of the placenta. Trophoblastic invasion results in complete replacement of endothelium by a layer of trophoblastic cells. The medial coat of the vessel, which consists of smooth muscle cells and connective tissue, is completely replaced by the invading trophoblasts. At the end of this remodeling, the spiral artery is made of a thin adventitial layer internally lined by trophoblasts; it is considerably dilated in diameter and is known as the uteroplacental vessel.

It has been suggested that trophoblastic invasion occurs in two phases. The first phase extends from the time of implantation until the 10th to 12th week of gestation; invasive growth progresses to two-thirds depth in the decidua. The second phase extends from the 12th week to the 16th to 18th week of gestation. The vessels are remodeled up to the terminal resistance portion of the vessel into the myometrial layer; this results in a marked decrease in the resistance to the blood flow into the uteroplacental vessels and into the intervillous space. As placentation progresses, trophoblastic invasion incorporates greater numbers of vessels, until an average of 100 decidual arteries are tapped for intervillous circulation. In patients who eventually develop preeclampsia, the invasion depth in the second-phase trophoblastic invasion might be deficient. The insufficient depth allows greater numbers of decidual spiral arteries to retain the resistance portion of the vessel, which prevents adequate dilation of these vessels. More important, the contractile portion of these vessels remains intact, which has profound implications for the effect of vasomotor regulators of circulation.

VASOMOTOR REGULATION OF UTEROPLACENTAL CIRCULATION

Regulation of Uterine Blood Flow

It is now recognized that many organs have mechanisms for regional regulation of blood flow. The uterus is similar to the kidney in its embryologic origin, anatomic vascular arrangement, and mechanisms for regulation of blood flow. Similar to the kidney, uteroplacental circulation produces various vasodilators and vasoconstrictors, including eicosanoids, endothelin, nitric oxide, renin, and angiotensinogen. Various aberrations occur in these vasomotor regulators in preeclampsia. Prostaglandin production has been shown to be decreased in preeclampsia; however, such deficiency accounts for only a small degree of change in blood pressure (3 to 5 mm Hg). Thromboxane is considered a counter-regulatory vasoconstrictor eicosanoid to prostacyclin, and its production has been shown to be increased. Viewing these two facts together, the balance of eicosanoids could be disturbed in preeclampsia. Some investigators have suggested that endothelin levels may be increased in preeclampsia. Others have shown that it is not.

In experimental gravid animal models, pharmacologic interventions to decrease nitric oxide production are associated with development of systemic hypertension. Nitric oxide production by measurements of urinary metabolite has been shown not to be deficient in human preeclampsia, however.

Role of the Renin-Angiotensin System

The renin-angiotensin system might be involved in the pathogenesis of preeclampsia. The role of angiotensin II in regulating uterine blood flow directly or through alterations of eicosanoids has been suggested in experimental settings. Uterine venous angiotensin II levels are higher in hypertensive human pregnancy. More important, systemic vasculature becomes more responsive to angiotensin II in preeclampsia. In view of evidence for uteroplacental ischemia and evidence for local renin and angiotensinogen production in the uterus, it is reasonable to assume that uterine vasculature is also modified to become more sensitive to angiotensin II in human preeclampsia. This vascular maladaptation, i.e., increased responsiveness to angiotensin II and development of hypertension, was first described by Goldblatt similar pathophysiology. It has been shown in renin gene overexpression models with development of hypertension. This research on renin gene overexpression models with hypertension
emphasizes the role of renin in the evolution of vascular maladaptation.

The change in the vasculature in renin-mediated hypertension is primarily driven by functional changes in the vasculature. Such functional changes in vasculature in renin-mediated hypertension are biochemically mediated by alterations in the cyclooxygenase pathway of arachidonic acid metabolism and increased thromboxane production,100 protein kinase C-mediated mechanism and its effect on calcium handling by the vascular smooth muscle,50 alterations in the Na+/K+ pump and cotransport,92 and change in endothelin expression and release.7 Initial change in vasculature in renin-mediated vasoconstriction seems to be mediated through increased sympathoadrenal activity. Many of these alterations have been described in human preeclampsia,50,75 including increased sympathoadrenal activity.70

Takimoto and colleagues90 reported the development of preeclampsia-eclampsia syndrome by crossbreeding transgenic mice, with the introduction of human renin (Ren) and human angiotensinogen (AGT) genes into the mouse genome. Specifically, when male mice carrying human renin Ren and human angiotensinogen AGT, Ren were mated with female mice carrying human AGT, Ren preeclampsia syndrome developed, and renin overexpression was shown on the fetal side of the placenta. One important aspect of the mouse model of preeclampsia is that fetal renin from the placenta seemed to transfer to the maternal circulation much more readily than is reported in humans.36

In human preeclampsia, renin gene expression is increased in the decidua vera on the maternal side.73 Increased renin production from the uterus has been shown to occur in response to decreased blood flow to the uterus in experimental settings.102 Collectively, these data suggest a role of increased renin production in the uteroplacental interphase in the pathogenic mechanism of preeclampsia.

Increased heterodimerization of angiotensin AT1 and bradykinin B2 receptors has been described in preeclampsia.11a These investigators have suggested the concept that AT1-B2 heterodimerization mediates at least part of the increased responsiveness to angiotensin II in preeclampsia by using the B1 intracellular domain for the signal transduction.1a Susceptibility of AT1 homodimers to inactivation by peroxide treatment suggests that oxidative stress of normal pregnancy may confer some of the angiotensin II refractoriness.1a The mechanism by which the AT1-B2 heterodimerization is induced is not yet defined.

Patients with preeclampsia develop autoantibodies against the second loop of the AT1 receptor (AT1-AA)96 which might be another mechanism involved in AT1 receptor and adreno-receptor signaling. How an antibody against the AT1 receptor could cause signal transduction to occur through the α1 adrenoreceptor remains unexplained. These antibodies enhance the tissue factor expression in vitro with increased immunoreactivity for tissue factor in preeclamptic placentas.10 These data on AT1-AA correlate with the findings of anti-ssDNA and anti-dsDNA autoantibodies in preeclampsia,103 suggesting an abnormal or unrestrained B cell activation in preeclampsia or perhaps aberrantly increased antigen presentation, or both.

Angiotensinogen mutation with increased angiotensin II production and susceptibility to development of preeclampsia has been shown in some populations, but not in others.98 Because other biochemical aberrations that mediate vascular maladaptation are renin mediated, renin from uteroplacental interphase might have a role in initiating the pathogenesis of preeclampsia (Fig. 15–1).

In addition to development of systemic hypertension, alterations in regional organ circulation occur in sites that are normally renin-angiotensin dependent. This reduction in local blood flow could explain the spectrum of clinical manifestations of preeclampsia.

Vasomotor Implications of Vascular Modeling

The intactness of the resistance portion of the uteroplacental vessels with preserved ability for vasoconstriction should have profound implications for uteroplacental ischemia. These vessels should also become increasingly responsive to angiotensin II that is produced locally in the placenta. The local renin-angiotensin system could initiate vasoconstriction-mediated ischemia and cellular injury in the uteroplacental vascular bed.

**PATHOPHYSIOLOGIC BASIS OF CLINICAL MANIFESTATIONS**

The renin-angiotensin system is involved in physiologic regulation of blood flow in various organs, including the heart and systemic vasculature and the uterus, kidney, liver, and brain (Table 15-1). These are also the sites for major clinical manifestations of preeclampsia-eclampsia, which emphasizes the role of the renin-angiotensin system in the pathogenesis of this disorder. Clinical manifestations are described here according to the systemic or regional circulations involved. The primary mechanism at all sites is increased responsiveness to angiotensin II, leading to increased vascular resistance initially and vasoconstriction later with attendant hypoxemia and cell damage. When vasoconstriction and hypoxemia occur, endothelial dysfunction sets in, and free radical formation and lipid peroxidation may accelerate the process further.85,86 Endothelial dysfunction can occur earlier in individuals susceptible to such endothelial damage (e.g., thrombophilic conditions).34 Other studies suggest that such individuals might not be at an increased risk.52

![Figure 15–1. Renin-angiotensin system in pathogenesis of preeclampsia.](image-url)
SECTION III PREGNANCY DISORDERS AND THEIR IMPACT ON THE FETUS

Cardiovascular Manifestations
Increased sympathoadrenal activity may mediate increases in cardiac output. Increase in cardiac work demanded by increased cardiac output is generally well tolerated by young patients, but it may occasionally precipitate left ventricular failure. Decreased renal perfusion, high hydrostatic pressure owing to the cardiovascular changes, and decrease in oncotic pressure owing to proteinuria compounded by fluid overload may result in development of pulmonary edema.

Systemic vasculature is most frequently and fairly consistently involved with vasoconstriction, the primary manifestation being development of hypertension. Usually, systolic and diastolic blood pressures are elevated, and hypertension is proportional to renal manifestations, especially proteinuria, at least in uncomplicated cases. Hypertension to some degree depends on increased sympathoadrenal activity, which explains the fluctuations in blood pressure and accelerations related to anxiety.

High cardiac output in the face of markedly increased peripheral vascular resistance may result in traumatic intravascular hemolysis. This condition can cause a decreased haptoglobin level, increased free hemoglobin level, increased bilirubin levels, burr cells and schistocytes in the peripheral blood, and an increased free serum iron level.

Renal Manifestations
Proteinuria; elevated creatinine and decreased creatinine clearance; oliguria
Elevated uric acid
Renal tubular necrosis and renal failure

Cerebrovascular Manifestations
Generalized grand mal seizures ( eclampsia)
Cerebral hemorrhage
Coma
Central blindness; loss of speech

Hepatic Manifestations
Elevated liver enzymes
Intracellular fatty deposit

Hematologic Manifestations
Schistocyte burr cells; elevated free hemoglobin and iron; decreased haptoglobin levels
Thrombocytopenia; antiplatelet antibodies

TABLE 15–1 Findings and Clinical Manifestations of Preeclampsia

<table>
<thead>
<tr>
<th>Vasculature or System</th>
<th>Findings</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Increased cardiac output and systemic vasoconstriction</td>
<td>Systemic hypertension</td>
</tr>
<tr>
<td></td>
<td>Increased hydrostatic pressure</td>
<td>Generalized edema</td>
</tr>
<tr>
<td></td>
<td>High cardiac output and hypertension</td>
<td>Intravascular hemolysis</td>
</tr>
<tr>
<td>Uteroplacental</td>
<td>Uteroplacental insufficiency</td>
<td>Fetal somatic growth deficiency; fetal hypoxemia and distress</td>
</tr>
<tr>
<td></td>
<td>Decidual ischemia</td>
<td>Abruptio placentae; placental infarcts</td>
</tr>
<tr>
<td></td>
<td>Decidual thrombosis</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Renal</td>
<td>Decreased renal blood flow and glomerular filtration rate; endothelial damage</td>
<td>Proteinuria; elevated creatinine and decreased creatinine clearance; oliguria</td>
</tr>
<tr>
<td></td>
<td>High All responsiveness of tubular vasculature</td>
<td>Elevated uric acid</td>
</tr>
<tr>
<td></td>
<td>All of the above</td>
<td>Renal tubular necrosis and renal failure</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>Cerebral motor ischemia</td>
<td>Generalized grand mal seizures ( eclampsia)</td>
</tr>
<tr>
<td></td>
<td>High cerebral perfusion pressure with regional ischemia</td>
<td>Cerebral hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Cerebral edema</td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td>Regional ischemia</td>
<td>Central blindness; loss of speech</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Ischemia; hepatic cellular injury</td>
<td>Elevated liver enzymes</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial injury</td>
<td>Intracellular fatty deposit</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Intravascular hemolysis</td>
<td>Schistocyte burr cells; elevated free hemoglobin and iron; decreased haptoglobin levels</td>
</tr>
<tr>
<td></td>
<td>Decidual thrombosis, release of FDP</td>
<td>Thrombocytopenia; antiplatelet antibodies</td>
</tr>
</tbody>
</table>

AII, angiotensin II; FDP, fibrin degradation products.

Uterine Vasculature
Initially, high cardiac output and increased vascular resistance without change in vessel diameter may result in increased uteroplacental perfusion. Later, with a marked increase in local vasoconstriction, regional blood flow would decrease.

Uteroplacental ischemia and placental infarcts are well-recognized pathologic findings of preeclampsia-eclampsia syndrome. Decreased uteroplacental blood flow explains increased frequency of somatic growth deficiency in this condition (see also Chapter 14). Severe reductions in uteroplacental blood flow can cause fetal hypoxemia, which is clinically manifested as fetal distress, hypoxic multiorgan failure, or death. Uteroplacental interface hypoxemia can also result in cellular injury to the decidua and injury to the vascular wall itself, with resultant small hemorrhages.

Two processes—hypoxemic cell injury and hemorrhage—sometimes cause small disruptions of placental attachment, which cause further disruption of the vascular wall as a result of the mechanics of physical separation. Disruption of the vascular wall causes bleeding in the uteroplacental interface; this may explain development of abruptio placentae.
Uteroplacental interface vessels normally have fibrin deposition, a process that can be aggravated by vasoconstriction, and further decreases in the blood flow in these vessels. These reductions in blood flow explain the decidual thrombosis and initiation of thrombocytopenia with local platelet consumption. Dissemination of small fibrin degradation products from these vessels and release of tissue thromboplastin from decidual and trophoblast cell injury can cause disseminated intravascular coagulopathy.

**Renal Vasculature**

Decreased renal blood flow and high renal perfusion pressure and associated hypoxemia can cause glomerular injury, which causes proteinuria. Glomerular injury may be associated with fibrin deposits in the basal layer and swelling of endothelial cells, resulting in glomerular endotheliosis seen in renal histology. A severe decrease in renal blood flow can cause oliguria, and severe vasoconstriction and hypoxemia with cellular injury might explain renal tubular necrosis seen occasionally in preeclampsia.

Excess circulating placental soluble fms-like tyrosine kinase 1 (sFlt-1), an antagonist of vascular endothelial growth factor (VEGF) and placental growth factor, has been shown in preeclampsia. By reducing the circulating levels of VEGF and placental growth factor, sFlt-1 may contribute to the endothelial dysfunction and impaired renal vasorelaxation. This sFlt-1 is a splice variant of VEGF receptor-1 (VEGFR-1); it is produced by the placenta and has been known to enter the maternal circulation. Administration of sFlt-1 to pregnant rats induced hypertension, proteinuria, and glomerular endotheliosis. Recent experimental evidence showing attenuation of hypertension and decrease in renal injury by infusion of recombinant VEGF 121 in a rat model further validates the role of sFlt-1 in the pathogenesis of preeclampsia. Similarly, soluble endoglin, a novel placenta-derived soluble transforming growth factor-β coreceptor, seems to contribute to the pathophysiology by dysregulating signaling in the vasculature.

Decreased renal tubular blood flow (this vasculature is sensitive to angiotensin II) results in proximal tubular exchange of urate in favor of plasma, which explains frequent association of elevated serum uric acid as a manifestation of preeclampsia. Elevated uric acid more accurately reflects an increase in plasma urate and reflects an increase in plasma uric acid. A severe decrease in renal blood flow can cause oliguria, and severe vasoconstriction and hypoxemia with cellular injury might explain renal tubular necrosis seen occasionally in preeclampsia.

Excess circulating placental soluble fms-like tyrosine kinase 1 (sFlt-1), an antagonist of vascular endothelial growth factor (VEGF) and placental growth factor, has been shown in preeclampsia. By reducing the circulating levels of VEGF and placental growth factor, sFlt-1 may contribute to the endothelial dysfunction and impaired renal vasorelaxation. This sFlt-1 is a splice variant of VEGF receptor-1 (VEGFR-1); it is produced by the placenta and has been known to enter the maternal circulation. Administration of sFlt-1 to pregnant rats induced hypertension, proteinuria, and glomerular endotheliosis. Recent experimental evidence showing attenuation of hypertension and decrease in renal injury by infusion of recombinant VEGF 121 in a rat model further validates the role of sFlt-1 in the pathogenesis of preeclampsia. Similarly, soluble endoglin, a novel placenta-derived soluble transforming growth factor-β coreceptor, seems to contribute to the pathophysiology by dysregulating signaling in the vasculature.

**Hepatic Vascular Changes**

Angiotensin II responsiveness of hepatic vasculature is well recognized; it has been used for selective chemotherapy for tumors by angiotensin II infusion-induced vasoconstriction of normal vasculature to protect normal liver tissue. In later phases of disease, hepatic vasoconstriction-mediated hypoxemia and cellular injury are expected to result in release of hepatic enzymes into the circulation, with elevation of liver enzymes in blood. Hepatic vasculature in the subcapsular region seems particularly susceptible to injury, resulting in small hemorrhages. In combination with disseminated intravascular coagulopathy, these hemorrhages can become larger and cause major subcapsular hematomas of the liver. Tissue injury with edema of liver parenchyma and capsule and with stretching of the capsule could explain the hepatic origin of epigastric pain.

HELLP syndrome is a combination of intravascular hemolysis, elevated liver enzymes, and thrombocytopenia or low platelets. Acute fatty liver of pregnancy (AFLP) is a condition with a predominantly hepatic manifestation; it is frequently associated with thrombocytopenia and frequently occurs without cardiovascular manifestations of preeclampsia. Cellular hypoxemic injury explains mitochondrial damage, disruption of fatty acid metabolism, and deposition of microvesicular fat in hepatic cells. Susceptible women (women with a carrier state of deficiency of enzymes of fatty acid metabolism and short-chain and long-chain fatty acid dehydrogenase) might develop AFLP. In most cases, AFLP occurs independent of preeclampsia. There seems to be some overlap in the pathophysiology of AFLP and preeclampsia with AFLP; hepatic manifestations predominate in individuals with such susceptibility. Mitochondrial enzyme defects may occur as gene defects or be acquired through cell injury mediated by free radicals.

**Central Nervous System**

High cardiac output and increased vascular resistance may be associated with greater regional circulation in the brain at higher perfusion pressure. Some regions of the brain, especially in advanced stages of the disease, might have locally decreased perfusion.

Vasoconstriction and hypoxemia in the microvasculature of the brain result in cellular injury. The injury causes extra- cerebral release of intracellular sodium, which provides the means for generating aberrant electric impulses. The motor cortex seems to be particularly susceptible to such cellular injury, with resultant convulsions and eclampsia. Vasoconstriction of different regions of the brain produces different manifestations: Vasoconstriction in the frontal cortex causes frontal headache, constriction in the occipital cortex causes visual disturbances and central blindness, and constriction in the Broca area causes loss of speech. Blindness may also develop as a result of retinal detachment. Most patients who develop blindness recover completely without medical intervention. In cases of cerebral edema, coma and loss of recent memory of specific convulsive episodes occur.

Cerebrovascular accidents occur as a result of cerebral vasospasm, hypoxemia-induced vascular damage, and systemic hypertension that causes mechanical rupture or disruption of the vessel wall. Current data in developed countries suggest that almost 70% of hypertension-related maternal mortality is due to cerebrovascular accidents. Data on stroke and severe preeclampsia and eclampsia suggest a paradigm shift to focus on reduction in systolic blood pressure. Hyperreflexia has been recognized as a sign of neurologic irritability in epilepsy and is seen before eclamptic seizures, but many women have normally active deep tendon reflexes without neurologic irritability.
Clinical Considerations

PREDISPOSING FACTORS

Several factors are associated with, or suggested to be associated with, an increased risk of preeclampsia-eclampsia, as follows:

Parity: Eclampsia and preeclampsia are recognized to occur more frequently in the first pregnancy.  
Age: Relationship to age is described as a J-shaped curve with slightly increased incidence in young primigravidae and a more pronounced increased incidence in older primigravidae. 
Race: Incidence of hypertension is not increased in African Americans, in contrast to a commonly held belief, although a higher incidence of proteinuria is observed. 
Family: In a study of women with eclampsia, their daughters had an incidence of preeclampsia of 26%, their sisters had an incidence of 37%, and their daughters-in-law had an incidence of 8%. 
Genetics: Genetic predisposition has been suspected on the basis of increased familial incidence, suggesting a recessive trait possibly of maternal origin. 
Diet: Most studies suggest that protein, carbohydrate, or total calorie intake does not influence the incidence of preeclampsia. 
Social status: Several reports suggest that populations with lower socioeconomic status have a higher incidence of preeclampsia and severe preeclampsia. 
Twin pregnancies: Twinning is associated with a higher incidence of preeclampsia compared with singleton gestation. Severe preeclampsia occurs more frequently in monzygotic twinning, especially in multiparous women. 
Diabetes: The incidence of preeclampsia is generally thought to be increased in diabetic pregnancies. 
Hydatidiform mole: The higher incidence and early onset of preeclampsia are well recognized in molar gestation, these features are also observed in triploidy gestations, which usually have partial mole. 
Hydrops fetalis: The incidence of preeclampsia seems to be increased only in nonimmune hydrops fetalis. 
Polyhydramnios: Increased incidence of preeclampsia observed in association with polyhydramnios is related to causes of polyhydramnios, including multiple gestation, diabetes, and hydrops fetalis. 
Climate and season: Despite considerable interest and analysis, climatic and seasonal factors do not seem to contribute to the incidence of preeclampsia. 
Cigarette smoking: The incidence of preeclampsia is lower in smokers compared with nonsmokers. If preeclampsia does occur, however, fetal risks are greater in smokers compared with nonsmokers. 

Although susceptibility to preeclampsia might be increased by maternal thrombophilic mutations, most of the data have been inconclusive and contradictory. A more recent case-control study suggests, however, that prevalence of factor V and factor II mutations is increased in patients with preeclampsia without a previous thromboembolic disorder. Researchers have suggested that the thrombophilic mechanism might interact with other pathogenic factors to determine clinical features of the disease.
or edema provides corroborating background. In a few patients, the disease process may progress so rapidly that convulsions might occur without proteinuria or before proteinuria develops.

**VARIABILITY IN PROGRESSION OF PREECLAMPSIA**

A well-recognized characteristic of preeclampsia is the variability in progression of the disease (Fig. 15-2). It is necessary to establish an algorithm for each individual case to monitor progression. Figure 15-2 graphically depicts various scenarios of the progression of preeclampsia, indicating that the clinician may encounter these patients at different stages of the disease process. At point A, all patients have similar degrees of severity, such as mild preeclampsia. If delivery is not undertaken because of prematurity, the monitoring algorithm should initially consider the possibility of rapid progression. If rapid progression is not observed in 24 to 48 hours, frequency of laboratory testing and monitoring of other parameters can be reduced until some clinical signs are detected that suggest acceleration of the disease process. Clinically, this can manifest as acceleration of hypertension or development of increasing facial edema along with glistening sheen, known as toxemic facies. When such a change is observed clinically, additional testing of laboratory parameters might be necessary to reevaluate the patient.

**SEVERITY OF PREECLAMPSIA**

Preeclampsia can be categorized for its severity, arbitrarily defined as mild or severe; in clinical settings it might also be reasonable to consider moderate severity. Severe preeclampsia is defined based on the following criteria:

- Systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 110 mm Hg
- Proteinuria of 5 g or more per 24 hours (3+ or 4+ on urine dip strip examination)
- Oliguria defined as urine output of 500 mL or less in 24 hours
- Visual disturbances, particularly scotomata (black spots or flashes)
- Epigastric pain

**Indications for Delivery**

The following are indications for delivery:

- Preeclampsia of any severity at term
- Moderately severe preeclampsia near term (i.e., after 34 weeks’ gestation)
- Eclampsia at any gestational age
- Rapidly progressive preeclampsia with secondary system involvement, such as thrombocytopenia and elevated liver enzymes, at any gestational age
- Clinical unequivocal evidence of fetal compromise, such as persistent nonreactive nonstress test, poor biophysical profile score, or spontaneous repetitive decelerations in fetal heart rate monitoring, at any gestational age
- Established evidence of fetal pulmonary maturity

**Intrapartum Treatment**

**ANTIHYPERTENSIVES**

Severe hypertension has serious cerebrovascular consequences in terms of parenchymal ischemia and hemorrhage. Decisive treatment of hypertension is indicated for hypertensive episodes. Such blood pressure criteria are generally a diastolic pressure of greater than 105 mm Hg or systolic pressure 160 mm Hg or greater.
Sublingual nifedipine and an intravenous bolus of hydralazine are the primary antihypertensives used. The results of meta-analysis of randomized, controlled trials are not robust enough to guide clinical practice, but they do not support use of hydralazine as first-line treatment of severe hypertension in pregnancy; labetalol and nifedipine show most promise, but clinical trials are needed. There is no evidence of inadvertent precipitation of angina and myocardial infarction with use of sublingual nifedipine in this generally healthy young population. Caution is indicated, however, with use of nifedipine for older mothers (40 years old and older) when there is a family history of coronary artery disease at a young age and especially in women who are heavy smokers. Labetalol and clonidine have also been used for the same purpose (Table 15-2).

### CORTICOSTEROIDS
Evidence supports use of glucocorticoids safely in patients with preeclampsia for accelerating fetal pulmonary maturation.

### Method of Delivery
Cesarean section is best reserved for specific obstetric clinical indications. Availability of cervical ripening agents containing prostaglandins makes the success of vaginal delivery more feasible. Vaginal delivery after induction of labor is the mainstay method for patients with preeclampsia and most cases of eclampsia because induction of labor in patients with preeclampsia may be easier than predicted by cervical findings.

### Seizure Prophylaxis and Treatment of Eclampsia
Magnesium sulfate infusion for prevention of seizures is routinely recommended by most authorities in the United States. This recommendation is made partly because the signs and symptoms of preeclampsia are unreliable predictors of eclampsia, and partly because magnesium sulfate infusion is remarkably safe prophylaxis. Several other agents have been used for seizure prophylaxis, including phenytoin. An international randomized trial now supports use of magnesium sulfate, however, as the agent of choice over phenytoin for such prophylaxis.

Magnesium sulfate is well recognized as the treatment for preventing further seizures in patients presenting with eclampsia. Magnesium sulfate can be used safely even in patients taking nifedipine (a calcium channel blocker) because there is no evidence of adverse consequences, and there is no sound theoretical basis for avoiding such a combination.

The most commonly used regimen of magnesium sulfate is intravenous infusion given as a 2- to 4-g bolus over 5 to 30 minutes followed by continuous infusion starting at 1 g/h and increasing to 2 g/h to maintain therapeutic levels of 4 to 6 mEq/L. Intramuscular injection of magnesium sulfate has fallen out of favor because of pain associated with the injections and lack of precision in maintaining therapeutic levels. Close supervision of the patient's deep tendon reflexes and urine output measurements is important.

Serum magnesium concentrations in the neonate are very similar to the concentrations in the mother. Stone and Pritchard reported that Apgar scores do not correlate with magnesium levels. Clinical observations by neonatologists suggest higher frequency of neonatal hypotonia and decreased intestinal motility in infants exposed to magnesium sulfate (see also Chapter 49, Part 2).

### Prevention of Preeclampsia
Until all aspects of the pathogenic mechanisms are well defined, prevention of preeclampsia remains an unrealized goal. Studies of aspirin and calcium supplementation have not supported their use in either low-risk or high-risk populations. Selective use of aspirin in conditions where suppression of platelet activation may be beneficial includes antiphospholipid antibody syndrome.

| TABLE 15–2 Pharmacotherapy for Maternal Hypertensive Emergencies |
|---------------------|-----------------|----------------|
| Drug               | Initial Dose    | Repeat Doses   | Comments and Precautions |
| Hydralazine (bolus)| 5 mg IV bolus; response time 10-15 min | 5-10 mg every 20-30 min | If no response with total dose of 20 mg, consider alternatives |
| Hydralazine (infusion)| 40 mg in 500 mL D5/LR; begin at 15-25 mL/h | Begin at 1 mL/min, titrate against blood pressure |
| Nifedipine         | 10 mg sublingual, response time 10 min with maximum effect at 30 min | 10 mg in 30 min | If no response after 20 mg, consider alternatives; avoid in elderly patients or in patients with family history of coronary disease, especially if smokers |
| Clonidine          | 0.1 mg PO      | 0.1 mg in 30 min, then 0.1 mg every h | Patient must be placed on equivalent maintenance dose tid |
| Labetalol          | 20 mg IV bolus, response time 5-10 min | 20 mg dose or begin infusion of 1-2 mg/min | Check cardiac functional suppression |

D5/LR, 5% dextrose in lactated Ringer’s solution.
It has been suggested that there is an increased risk for developing hypertension later in life in women who develop preeclampsia in their first pregnancy. This misconception is due to erroneously including chronic hypertensive disorders in the preeclamptic patients being studied. Long-term follow-up studies of preeclampsia-eclampsia in the first pregnancy by Chesley and coworkers suggest there was no increase in the rate of hypertension. Multiparous women do exhibit excess rates of hypertension and cardiovascular mortality, however, which is best explained by underlying hypertensive disorders.

**OTHER HYPERTENSIVE DISORDERS**

**Gestational Hypertension**

Gestational hypertension typically occurs in the third trimester. Recurrence of nonproteinuric hypertension of this type in 15% to 25% of patients with hypertensive disorders suggests an underlying hypertensive disorder, especially if there is a family history of essential hypertension. Under such circumstances, and in the absence of signs and symptoms of preeclampsia, antihypertensive treatment should be considered. Such antihypertensive therapy may reduce the need for hospitalization, and makes outpatient monitoring and management easier. Patients managed as outpatients benefit from ambulatory blood pressure monitoring.

Antihypertensive treatment is similar to that for patients with chronic hypertension. Acceleration of hypertension or need for progressively increasing antihypertensive therapy may indicate development of superimposed preeclampsia or misdiagnosis of the condition as transient hypertension. Careful evaluation of signs and symptoms of preeclampsia before beginning antihypertensive therapy can minimize such difficulties. Patients with severe hypertension without evidence of preeclampsia might have severe hypertension because of cocaine abuse. All patients with severe hypertension manifesting in an episodic manner should have a toxicology urine screen test for accurate diagnosis and appropriate treatment of hypertension and substance abuse.

**Chronic Hypertension**

Chronic hypertension in pregnancy is hypertension (i.e., blood pressure greater than 140/90 mm Hg) diagnosed before the 20th week of gestation or hypertension before pregnancy. Overt hypertension is easily diagnosed, but latent hypertension does not become apparent until later in pregnancy. Latent hypertension is frequently misdiagnosed as transient hypertension.

**CLASSIFICATION**

Hypertension in pregnancy is classified as primary, secondary, or chronic (Box 15-1). Primary (essential or idiopathic) hypertension is the most common type observed; secondary hypertension is secondary to a known cause. Causes of secondary hypertension include renal parenchymal disease and renal vascular disease, adrenal diseases, coarctation of the aorta, and thyrotoxicosis. Renal parenchymal disease is the second most common cause of chronic hypertension; other causes are rare.
A complete urinalysis for protein and for microscopic sediment should be performed to diagnose renal disease. A 24-hour urinalysis for protein and determination of creatinine clearance should be performed to assess renal function. Serum electrolyte levels to rule out primary hyperaldosteronism should be checked only if the diagnosis is not obviously essential hypertension or renal disease.

If blood pressure elevation is episodic and reaches systolic pressures of 180 mm Hg and diastolic pressures greater than 110 mm Hg, urinary catecholamines should be measured to rule out pheochromocytoma. These patients should also have a toxicology screen.

Ultrasonography of the kidneys may be considered when clinically relevant (e.g., chronic pyelonephritis) to assess renal size and pelvic dilation if the patient did not have a diagnostic study before pregnancy. Electrocardiography and an echocardiogram can be considered depending on the severity of the hypertension.

**PRECONCEPTION COUNSELING**

If possible, counseling should be provided before conception to a woman who has chronic hypertension. This pre-conception counseling is important for establishing adequate control of hypertension and making changes in the antihypertensive regimen. It is important to establish baseline data and to teach self-monitoring of blood pressure. If the patient is taking diuretic medication, she should be advised that she should discontinue use of this medication before conception. An appropriate diet that curtails heavy salt use is recommended. Patients taking angiotensin-converting enzyme inhibitors should be advised to discontinue them because of serious risks of fetal defects and pregnancy loss.

**MANAGEMENT DURING PREGNANCY**

Bed rest is suggested to increase uterine blood flow and promote nutrition to the fetus. Uterine size and compression of the inferior vena cava and aorta are factors that alter blood pressure recordings in the supine position in the third trimester. The currently recommended position for outpatient blood pressure measurement, as advocated by the American Heart Association, is the sitting position. The brachial artery blood pressure is highest when sitting, lower when lying on the back, and lowest when lying on the side.

**Home Blood Pressure Monitoring**

All patients with chronic hypertension benefit from self-monitoring of blood pressure. Self-monitoring reduces use of antihypertensives and need for hospitalization. Self-monitored blood pressure readings tend to be lower, and they also reflect patients’ blood pressure readings in their environment more accurately. It is advisable to take blood pressure measurements at least three times a day. If the patient works outside the home, blood pressures should be taken during the work week and weekend. This practice identifies the effects of the environment on blood pressure.

Newer digital blood pressure monitors are easy to use and moderately inexpensive. For these reasons, the sphygmomanometer and stethoscope for self-monitoring can be abandoned. It is important to check calibration of the patient’s machine in the office.

**Other Considerations**

Therapeutic abortion is generally not necessary or recommended, but the decision regarding whether to continue the pregnancy should be determined on an individual basis. It is essential to establish the estimated date of confinement. History, early pelvic examination, and early ultrasonography aid in this process. Ultrasonography is needed (at 3- to 6-week intervals from 24 to 28, 28 to 32, and 32 to 36 weeks) during pregnancy to detect intrauterine growth restriction, which is most likely to develop after the 30th week of gestation.
Pharmacotherapy

There is a general consensus that severe hypertension should be treated to reduce maternal risks of cerebral vascular complications. Meta analysis of several small trials suggests that treatment of mild and moderate hypertension reduces the occurrence of severe hypertension and repeat hospitalizations later in pregnancy.1

There is no current proof that pharmacotherapy (Table 15-3) alters fetal salvage or prevents preeclampsia, but it does control major accelerations of maternal blood pressure during pregnancy. This control might reduce the risk of complications of severe hypertension, especially cerebrovascular accidents. Anti-hypertensive medication should be started when home diastolic blood pressure consistently exceeds 94 mm Hg or office blood pressure readings consistently exceed 90 mm Hg.

Pharmacologic agents inhibiting renin-angiotensin system (angiotensin converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor inhibitors) are classified by the FDA as class D with the black box warning about their association with fetal growth restriction, fatal neonatal renal failure, and fetal anomalies with exposure during the second trimester. ACE inhibitors have recently been shown to be associated with major congenital malformations after exposure during the first trimester and are contraindicated anytime during pregnancy.8a ACE inhibitors are important for diabetic patients with nephropathy and should be prescribed after delivery along with effective contraception.86a

The current drug of choice is methyldopa (Aldomet).55 Since the mid-1980s, beta blockers such as propranolol or atenolol have been used.69 These agents increase the risk of intrauterine growth restriction, however, and might increase fetal morbidity. Alternative drugs include calcium channel blockers,6 clonidine, and labetalol.27,77 An analysis of clinical trials of beta blockers indicates that the effect of these agents on perinatal outcome is uncertain; the worrying trend toward an increase in infants who are small for gestational age is partly dependent on one small outlying trial.40 All drugs may cross the placenta; however, except for angiotensin converting enzyme inhibitors, these drugs have not been shown to cause birth defects.25,58

One should avoid using two antihypertensives of the same class whenever a patient needs more than one agent to control hypertension. This situation is most likely to occur for agents acting on the adrenergic system (e.g., combining methyldopa with labetalol should be avoided). It is better to use a vasodilator, such as nifedipine, as a second agent. Until better evidence is available, the choice of an antihypertensive should depend on the experience and familiarity with a particular drug, and on what is known about adverse maternal and fetal side effects, with the exception of diazoxide and ketanserin, both of which are probably not good choices.15 Labetalol and long-acting nifedipine are becoming the most commonly used antihypertensive agents in pregnant women. It is hoped that current trials in progress or in process of being launched will provide further clinical evidence-based guidelines.

Complications

Chronic hypertension is associated with a fourfold to eightfold increase in the incidence of abruptio placenta. Planned delivery at or near term may be advisable. The patient should be observed for preeclampsia as indicated by an increase in blood pressure and development of proteinuria. The patient should be hospitalized if preeclampsia is suspected.

ANTEPARTUM FETAL EVALUATION

Antepartum fetal evaluation includes serial ultrasound examinations to diagnose intrauterine growth restriction. Beginning at 32 weeks of gestation, nonstress tests should be performed twice a week, and fetal movement activity counts should show at least four movements per hour or three movements in 30 minutes, indicating fetal health.

LABOR AND DELIVERY

If a decision is made to proceed to delivery, and the cervix is not favorable for induction of labor, prostaglandin may be administered vaginally. Continuous electronic fetal monitoring should be performed during labor. Regional analgesia with epidural administration is ideal, as is also the case for patients with preeclampsia. It is recommended that a pediatrician be available for evaluation of the newborn.

SUMMARY

Women who have chronic hypertension usually do well during pregnancy, although 5% to 10% have major catastrophic events. Patients with chronic hypertension may take oral contraceptives postpartum; a barrier form of contraception is an alternative. For women who have completed their childbearing, a permanent form of contraception may be desirable.

<table>
<thead>
<tr>
<th>TABLE 15–3 Common Antihypertensive Agents for Chronic Hypertension in Pregnancy</th>
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<tbody>
<tr>
<td>Agent</td>
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<tr>
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</tr>
<tr>
<td>Methyldopa</td>
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<tr>
<td>Clonidine</td>
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<tr>
<td>Nifedipine XL</td>
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<tr>
<td>Amlodipine besylate (Norvasc)</td>
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<tr>
<td>Labetalol</td>
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XL, long-acting.
Superimposed Preeclampsia-Eclampsia

Superimposed preeclampsia-eclampsia is a condition that supervenes on a preexisting hypertensive disorder of any cause. Clinically, this is the most severe form of disease; it is associated with the most severe degree of hypertension and proteinuria. A diagnosis of superimposed preeclampsia generally indicates a need for expedited delivery. Establishment of baseline data on renal and other functions during the prenatal course is helpful for comparison. Usually, liver function abnormality indicates superimposed preeclampsia; however, association of methyldopa with elevation of liver enzymes without development of superimposed preeclampsia is known to occur. When such a diagnosis is under consideration, hospitalization is essential for evaluation, close supervision, monitoring, and delivery.

REFERENCES


28. Li Z, Zhang Y, Ying Ma J et al: Recombinant vascular endothelial growth factor 121 attenuates hypertension and improves...