

Hypertensive Disorders in Pregnancy

There are five types of hypertensive disease:.

Gestational hypertension

BP $\geq 140/90$ mm Hg for first time during pregnancy

No proteinuria

BP returns to **normal < 12 weeks'** postpartum

Final diagnosis made only postpartum

May have other signs or symptoms of preeclampsia, (epigastric discomfort or thrombocytopenia)

Preeclampsia

Minimum criteria

BP $\geq 140/90$ mm Hg after 20 weeks' gestation

Proteinuria ≥ 300 mg/24 hours or $\geq 1+$ dipstick

Increased certainty of preeclampsia

BP $\geq 160/110$ mm Hg, Proteinuria ≥ 2.0 g/24 hours or $\geq 2+$ dipstick

Serum creatinine > 1.2 mg/dL unless known to be previously elevated

Microangiopathic hemolysis (increased LDH)

Elevated ALT or AST, Platelets $< 100,000/\text{mm}^3$

Persistent headache or other cerebral or visual disturbance

Persistent epigastric pain

Eclampsia Seizures that cannot be attributed to other causes in a woman with preeclampsia

Superimposed Preeclampsia (on chronic hypertension)

New-onset proteinuria ≥ 300 mg/24 hours in hypertensive women but no proteinuria before 20 weeks' gestation

A sudden increase in proteinuria or blood pressure or platelet count $< 100,000/\text{mm}^3$ in women with hypertension and proteinuria before 20 weeks' gestation

Chronic Hypertension

BP $> 140/90$ mm Hg before pregnancy or diagnosed before 20 weeks' gestation not attributable to gestational trophoblastic disease or

Hypertension first diagnosed after 20 weeks' gestation and persistent after 12 weeks' postpartum

Preeclampsia

- Preeclampsia is a form of hypertension that is unique to human pregnancy. The clinical findings of preeclampsia can manifest as either a **maternal syndrome** (hypertension and proteinuria with or without other multisystem abnormalities) or as a **fetal syndrome** (fetal growth restriction, reduced amniotic fluid, and abnormal oxygenation).
- In practice, the maternal syndrome of preeclampsia represents a clinical spectrum with major differences between near-term preeclampsia without demonstrable fetal involvement versus preeclampsia that is associated with low birth weight and preterm delivery. **Preeclampsia is clearly a heterogeneous** condition for which the pathogenesis could be different in women with various risk factors.
- The pathogenesis of preeclampsia in nulliparous women **may be different than that in women with preexisting vascular disease, in multifetal gestation**, in diabetes mellitus, or previous preeclampsia. In addition, the pathophysiology of preeclampsia with early onset may be different than that of preeclampsia developing at term, during labor, or in the postpartum period.
- The incidence of preeclampsia ranges **between 2 and 7 percent in healthy nulliparous women**. In these women, preeclampsia is generally mild, with the onset near term or intrapartum **(75 percent of cases)**, and the condition conveys only a minimally increased risk for adverse pregnancy outcome. In contrast, the incidence and severity of preeclampsia are substantially higher in women with multifetal gestation, chronic hypertension, previous preeclampsia, pre-gestational diabetes mellitus, and in those with preexisting thrombophilias.
- Several risk factors have been identified with increased risk of preeclampsia. Generally, preeclampsia is considered a disease of **primigravid women**. The risk increases in those who have **limited sperm exposure** with the same partner before conception.
- The protective effects of long-term sperm exposure with the same partner might provide an explanation for the high risk of preeclampsia in **women younger than 20 years old**. A previous abortion (spontaneous and induced) or a previous normal pregnancy with the same partner is associated with a lower risk of preeclampsia. However, this protective effect is lost with a change of partner.
- Both Scandinavian and studies in this country have confirmed the importance of paternal factors, that is, the so-called **dangerous father**. Using whole population data, Lie et al. demonstrated that men who fathered one preeclamptic pregnancy were nearly twice as likely to father a preeclamptic pregnancy in a different woman (1.8; 95 percent confidence interval [CI] 1.2 to 2.6; after adjustment for parity), regardless of whether the new partner had a preeclamptic pregnancy in the past or not.

- Thus, mothers had a substantially increased risk in their second pregnancy (2.9 percent) if they were impregnated by a man who had fathered a preeclamptic first pregnancy with another woman. This risk was nearly as high as the average risk among first pregnancies.

Risk Factors for Preeclampsia

Age >40 years or <18 years

Nulliparity (RR 2.90)

Family history of preeclampsia (RR 2.91)

Obesity

Multifetal gestation (RR 2.93)

Preeclampsia in previous pregnancy

Prolonged interpregnancy interval

Woman herself was small for gestational age

Male partner whose mother or previous partner had preeclampsia

Hydrops fetalis

Unexplained fetal growth restriction

Poor outcome in previous pregnancy

Intrauterine growth retardation, abruptio, fetal death

Preexisting medical—genetic conditions

Chronic hypertension

Renal disease

Vascular or connective tissue disease

Type 1 (insulin-dependent) diabetes mellitus (RR 3.56)

Thrombophilias

Antiphospholipid antibody syndrome

Protein C, S, antithrombin deficiency

Factor V Leiden

- ☀ The recent advances in **assisted reproductive technology** have introduced several challenges for the maternal immune system that also increase the risk of preeclampsia. These include
 - 🌿 **Women older than 40 years,**
 - 🌿 **Infertile women during their first gestation or**
 - 🌿 **Obese women with polycystic ovary syndrome, and**
 - 🌿 **Women who become pregnant with donated gametes,** that is, donor insemination or oocyte donation, or embryo donation.
- ☀ The use of donated gametes can influence the maternal-fetal immune interaction. In addition, many of these women have multifetal gestations.
- ☀ Obesity is a definite risk for preeclampsia. Risk increases with increased body mass index. The worldwide increase in obesity is thus likely to lead to a rise in the frequency of preeclampsia. Obesity has a strong link with insulin resistance, which is a risk factor for preeclampsia. **The exact mechanism by which obesity/insulin resistance is associated with preeclampsia is not well understood**
- ☀ Women with early, severe preeclampsia (approximately 2 percent of cases in nulliparas) are at greatest risk of recurrence; rates of **25 to 65** percent have been reported. In women who had mild preeclampsia during the first pregnancy, the incidence of preeclampsia in a second pregnancy is **5 to 7 percent**, compared to **less than 1 percent** in women who had a normotensive first pregnancy (does not apply to abortions) [
- ☀ Advanced maternal age is an independent risk factor for preeclampsia (maternal age ≥ 40 **RR 1.96**, 95% CI 1.34-2.87 for multiparous women). Older women tend to have additional risk factors, **such as diabetes mellitus and chronic hypertension**. Whether adolescents are at higher risk of preeclampsia is more controversial; a systematic review did not find an association

Pathogenesis of preeclampsia

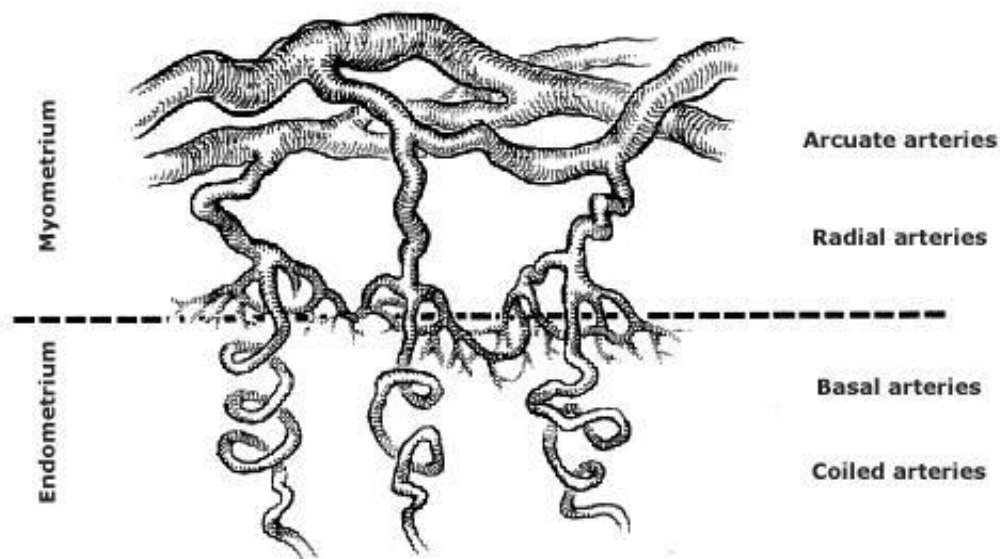
- ☀ The pathophysiology of preeclampsia likely involves both maternal and fetal/placental factors. Abnormalities in the development of placental vasculature early in pregnancy may result in relative placental **underperfusion/hypoxia/ischemia, which then leads to release of antiangiogenic factors into the maternal circulation** that alter maternal systemic endothelial function and cause hypertension and other manifestations of the disease.
- ☀ However, the molecular basis for placental dysregulation of these pathogenic factors **remains unknown**, and the role of angiogenic proteins in early placental vascular development are under investigation.
- ☀ Our current understanding of mechanisms causing the pathologic changes observed in preeclampsia will be reviewed here.

☀ **Abnormal development of the placenta** — The critical role of the placenta in the pathophysiology of preeclampsia is supported by epidemiologic and experimental data that show:

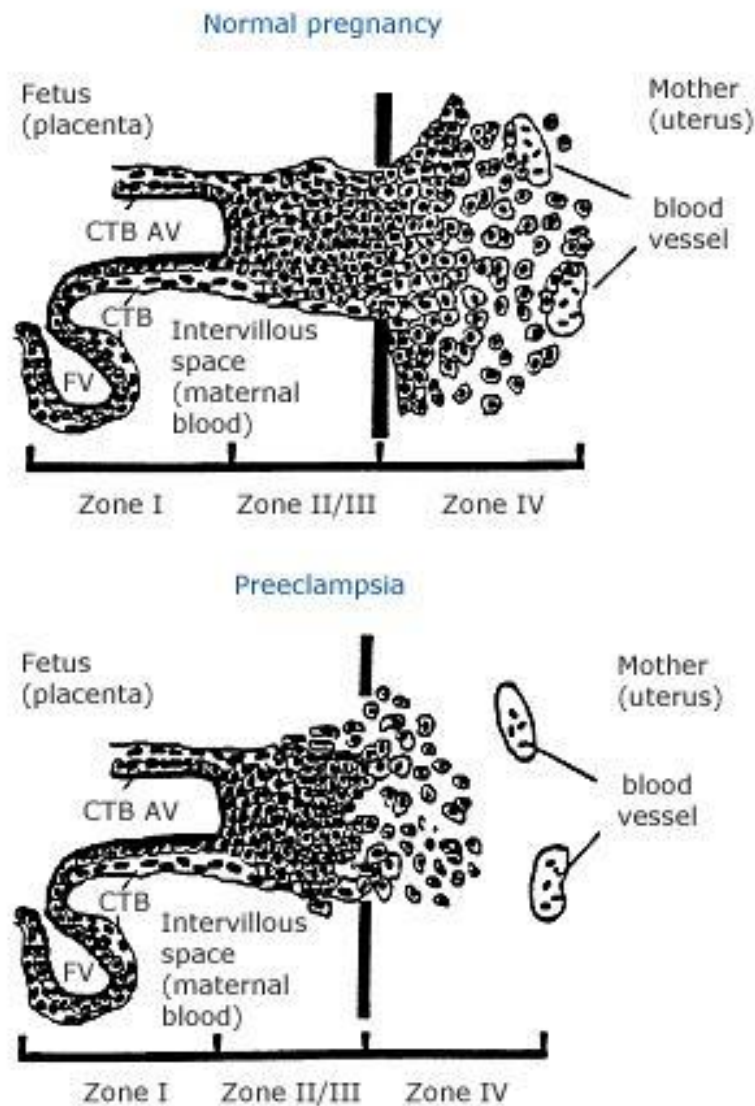
- ➡ Placental tissue is necessary for development of the disease, but the fetus is not.
- ➡ Preeclampsia is always cured after delivery of the placenta

☀ Examination of human placentas at various stages of gestation in women with normal pregnancies, as well as those with preeclampsia, has led to an understanding of normal placental morphology and pathologic changes in the uteroplacental circulation that are likely to be relevant to preeclampsia.

☀ **Abnormal remodeling of spiral arteries** — In normal pregnancies, the cytotrophoblast cells of the developing placenta migrate through the decidua and part of the myometrium to invade both the endothelium and highly muscular tunica media of the maternal spiral arteries, the terminal branches of the uterine artery that supply blood to the developing fetus/placenta. As a result, these vessels undergo transformation from small muscular arterioles to large capacitance vessels of low resistance, thus greatly facilitating blood flow to the placenta compared with other areas of the uterus. Remodeling of the spiral arteries probably begins in the late first trimester and is completed by 18 to 20 weeks of gestation, although the exact gestational age at which trophoblast invasion of these arteries ceases is unclear.



- By comparison, in preeclampsia, cytotrophoblast cells infiltrate the decidual portion of the spiral arteries, but fail to penetrate the myometrial segment. **The spiral arteries fail to develop into large, tortuous vascular channels created by replacement of the musculoelastic wall with fibrinoid material**; instead, the vessels remain narrow, resulting in placental hypoperfusion.



- The floating villi (FV) are in the intervillous space in direct contact with the maternal blood. In normal pregnancy, invasive **cytotrophoblasts (CTB) form cell columns (zone II/III) and invade maternal decidua and vasculature (zone IV)**. During the differentiation along the invasive path, the cytotrophoblasts dramatically alter their expression of various molecules, such as integrins. In preeclampsia, the invasive cytotrophoblasts fail to differentiate along the invasive pathway and do not gain access to spiral arteries.

☀ It is not known why the normal sequence of events in development of the uteroplacental circulation does not occur in some pregnancies. Vascular, environmental, immunological, and genetic factors all appear to play a role.

☀ **Defective trophoblast differentiation** — Defective differentiation of trophoblast is one possible mechanism responsible for defective trophoblast invasion of the spiral arteries. Trophoblast differentiation during endothelial invasion involves alteration in expression of a number of different classes of molecules, including cytokines, adhesion molecules, extracellular matrix molecules, metalloproteinases, and the class Ib major histocompatibility complex molecule, HLA-G. During normal differentiation, invading trophoblasts alter their adhesion molecule expression from those that are characteristic of epithelial cells (integrin **alpha6/beta1**, **alpha5/beta1**, and **E-cadherin**) to those of endothelial cells (integrin **alpha1/beta1**, **alpha5/beta1**, and **VE-cadherin**), a process referred to as pseudo-vasculogenesis. Trophoblasts obtained from women with preeclampsia do not show upregulated adhesion molecule expression or pseudo-vasculogenesis. The resulting impaired placentation and accompanying ischemia are thought to be the primary events leading to placental release of soluble factors that cause systemic endothelial dysfunction resulting in the preeclamptic phenotype.

☀ **Hypoperfusion, hypoxia, ischemia** — Hypoperfusion appears to be both a cause and a consequence of abnormal placental development. A causal relationship between poor placental perfusion, abnormal placental development, and preeclampsia is supported by the following examples:

1. Animal models that have successfully reproduced at least some of the findings of preeclampsia have involved mechanically reducing uteroplacental blood flow ,
2. Medical conditions associated with vascular insufficiency (eg, hypertension, diabetes, systemic lupus erythematosus, renal disease, acquired and inherited thrombophilias) increase the risk of abnormal placentation and preeclampsia , and
3. Obstetrical conditions that increase placental mass without increasing placental blood flow (eg, hydatidiform mole, hydrops fetalis, diabetes mellitus, and twin gestation) result in relative ischemia and are associated with preeclampsia.

☀ Hypoperfusion is also a result of abnormal placental development. Hypoperfusion becomes more pronounced as pregnancy progresses since the abnormal uterine vasculature is unable to accommodate the normal rise in blood flow to the fetus/placenta with increasing gestational age.

- ☀ Late placental changes consistent with ischemia include atherosclerosis (lipid-laden cells in the wall of the arteriole), fibrinoid necrosis, thrombosis, sclerotic narrowing of arterioles, and placental infarction. Although all of these lesions are not uniformly found in patients with preeclampsia, there appears to be a correlation between the severity of the disease and the extent of the lesions.
- ☀ Hypoperfusion, hypoxia, and ischemia is a critical component in the pathogenesis of preeclampsia because the hypoperfused, ischemic placenta elaborates a variety of factors into the maternal bloodstream that alter maternal endothelial cell function and lead to the characteristic systemic signs and symptoms of preeclampsia.
- ☀ **Immunologic factors** — the focus on immunologic factors as a possible contributor to abnormal placental development was based, in part, upon the observation that prior exposure to paternal/fetal antigens appears to protect against preeclampsia.
- ☀ Immunologic abnormalities, similar to those observed in organ rejection graft versus host disease, have been observed in preeclamptic women. The extravillous trophoblast (EVT) cells express an unusual combination of HLA class I antigens: HLA-C, HLA-E, and HLA-G. Natural killer (NK) cells that express a variety of receptors (CD94, KIR, and ILT) known to recognize class I molecules infiltrate the maternal decidua in close contact with the EVT cells. Interaction between NK cells and EVT cells has been hypothesized to control placental implantation. In preeclampsia, conflict between maternal and paternal genes is believed to induce abnormal placental implantation through increased NK cell activity.
- ☀ Placental bed biopsies from women with preeclampsia have revealed increased dendritic cell infiltration in preeclamptic decidual tissue. The dendritic cells are an important initiator of antigen-specific T-cell responses to transplantation antigens. It is possible that increased number of dendritic cells may result in alteration in presentation of maternal and fetal antigens at the decidual level, leading to either abnormal implantation or altered maternal immunologic response to fetal antigens.
- ☀ However, definitive evidence for this theory is lacking. Genetic studies looking at polymorphisms in the killer immunoglobulin receptors (KIR) on maternal NK cells and the fetal HLA-C haplotype suggest that women with KIR– AA genotype and fetal HLA-C2 genotype were at greatly increased risk of preeclampsia. A systematic review found no clear evidence that one or several specific HLA alleles were involved in the pathogenesis of preeclampsia. The authors suggested that interaction between maternal, paternal, and fetal HLA types, rather than any individual genotype alone, was probably an important factor to consider when studying immunogenetic determinants of preeclampsia.
- ☀ A more promising finding is that patients with preeclampsia have increased levels of agonistic antibodies to the angiotensin AT-1 receptor. This antibody can mobilize intracellular free calcium and may account for increased plasminogen activator 1 production and shallow trophoblast invasion seen in preeclampsia.

- ☀ In addition, angiotensin AT-1 receptor antibody stimulates sFlt-1 secretion. It is unclear if these **alterations are pathogenic or epiphenomena.**
- ☀ **Increased sensitivity to angiotensin II** — Increased sensitivity to angiotensin II has been described in preeclampsia, and may be related to increased bradykinin (B2) receptor upregulation in preeclamptic patients. Upregulation leads to heterodimerization of B2 receptors with angiotensin II type I receptors (AT1), and this AT1/B2 heterodimer increases responsiveness to angiotensin II in vitro.
- ☀ **Genetic factors** — although most cases of preeclampsia are sporadic, genetic factors are thought to play a role in disease susceptibility. A genetic predisposition to preeclampsia is suggested by the following observations:
 - ☀ Primigravid women with a family history of preeclampsia (eg, affected mother or sister) **have a two- to five-fold higher risk of the disease than primigravid women with no such history.**
 - ☀ The maternal contribution to development of preeclampsia can be partially explained by imprinted genes. In a study of sisters with preeclampsia, it was demonstrated that the mother developed preeclampsia only when the fetus/placenta inherited a maternal STOX1 missense mutation on **10q22**; when the fetus/placenta carried the imprinted paternal homolog, the preeclampsia phenotype was not expressed.
 - ☀ The spouses of men who were the product of a pregnancy complicated by preeclampsia are more likely to develop preeclampsia than spouses of men without this history. A woman who becomes pregnant by a man whose previous partner had preeclampsia is at higher risk of developing the disorder than if the pregnancy with the previous partner was normotensive.
 - ☀ These data suggest that both maternal and paternal contributions to fetal genes may have a role in defective placentation and subsequent preeclampsia. Several candidate genes, such as the angiotensinogen gene variant (T235), endothelial nitric oxide synthase (eNOS), and genes causing thrombophilia, have been linked with preeclampsia, but large studies have not shown them to be important for susceptibility to the disease.
 - ☀ Genome wide scanning of 343 Icelandic women with preeclampsia, eclampsia, and gestational hypertension revealed a significant locus at **2p13. Other susceptibility loci have been identified at 2p12, 2p25, and 9p13. The genes for sFlt-1 and Flt-1 are carried on chromosome 13.** Fetuses with an extra copy of this chromosome (eg, trisomy 13) should produce more of these gene products than their normal counterparts. In fact, the incidence of preeclampsia in mothers who carry fetuses with trisomy 13 is greatly increased compared to all other trisomies or to control pregnant patients. In addition, the ratio of circulating sFlt-1 to PlGF is significantly increased in these women, thus accounting for their increased risk of preeclampsia

- ☀ A different locus at 12q may be linked to HELLP syndrome, but not preeclampsia without HELLP syndrome, suggesting that genetic factors important in HELLP syndrome may be distinct from those in preeclampsia. However, discordant findings have also been reported. For example, a study of preeclampsia in twins failed to find a genetic link.
- ☀ **Diet** — The role of calcium and calcitropic hormones in the pathogenesis of preeclampsia is unclear

Systemic endothelial dysfunction

- ☀ All of the clinical features of preeclampsia can be explained as clinical responses to generalized endothelial dysfunction. As an example, hypertension results from disturbed endothelial control of vascular tone, proteinuria and edema are caused by increased vascular permeability, and coagulopathy is the result of abnormal endothelial expression of procoagulants. Headache, seizures, visual symptoms, epigastric pain, and fetal growth restriction are the sequelae of endothelial dysfunction in the vasculature of target organs, such as the brain, liver, kidney, and placenta.
- ☀ Laboratory evidence supporting generalized endothelial dysfunction in preeclamptic women includes the following:
 - 🌿 Increased concentrations of circulating cellular fibronectin, factor VIII antigen, and thrombomodulin.
 - 🌿 Impaired flow-mediated vasodilation and impaired acetylcholine mediated vasorelaxation.
 - 🌿 Decreased production of endothelial-derived vasodilators, such as nitric oxide and prostacyclin, and increased production of vasoconstrictors, such as endothelins and thromboxanes.
 - 🌿 Enhanced vascular reactivity to angiotensin II.
 - 🌿 Serum from preeclamptic women causes endothelial activation in human umbilical vein endothelial cell culture studies in some in vitro studies.
 - 🌿 Impaired endothelial function can be demonstrated by brachial artery flow-mediated dilation three years after a preeclamptic pregnancy. It is unknown whether this is a cause or effect of the preeclamptic pregnancy.
- ☀ The relationship between preexisting vascular disease and susceptibility to developing preeclampsia may be due to preexisting endothelial cell damage. Preexisting endothelial damage may also explain why women who develop preeclampsia are also at increased risk of developing cardiovascular disease later in life.

Pathogenesis of systemic endothelial dysfunction

- Mammalian placentation requires extensive angiogenesis for the establishment of a suitable vascular network to supply oxygen and nutrients to the fetus. A variety of **proangiogenic** (VEGF, PlGF) and **antiangiogenic factors** (sFlt-1) are elaborated by the developing placenta, and the balance among these factors is important for normal placental development. Increased production of antiangiogenic factors disturbs this balance and results in the systemic endothelial dysfunction characteristic of preeclampsia.
- sFlt-1, VEGF, PlGF — **Soluble fms-like tyrosine kinase 1 (sFlt-1 or sVEGFR-1) is a naturally occurring, circulating antagonist to vascular** endothelial growth factor (VEGF). VEGF is an endothelial specific mitogen that has a key role in promoting angiogenesis. Its activities are mediated primarily by interaction with two high-affinity receptor tyrosine kinases, VEGFR-1 (VEGF receptor-1 or fms-like tyrosine kinase-1 [Flt-1]) and VEGFR-2 (kinase-insert domain region [KDR]/Flk-1), which are selectively expressed on the vascular endothelial cell surface. VEGFR-1 has two isoforms: a transmembranous isoform and a soluble isoform (sFlt-1 or sVEGFR-1). Placental growth factor (PlGF) is another member of the VEGF family that is made predominantly in the placenta. It also binds to the VEGFR-1 receptor.
- **sFlt-1 antagonizes the proangiogenic biologic activity of circulating VEGF and PlGF by binding to them and preventing their interaction with their endogenous receptors.** Increased placental expression and secretion of sFlt-1 appear to play a central role in the pathogenesis of preeclampsia.
- **Soluble endoglin** — It is likely that synergistic factors elaborated by the placenta other than sFlt-1 also play a role in the pathogenesis of the generalized endothelial dysfunction noted in preeclampsia. **Consistent with this hypothesis is the observation that the plasma concentration of sFlt-1 protein** needed to produce the preeclampsia phenotype in rats was several fold higher than the levels typically seen in patients with preeclampsia, and no coagulation or liver function abnormalities were reported in the sFlt-1 treated animals.
- Eng is a coreceptor for transforming growth factor (TGF)-**beta and is highly expressed on cell membranes of vascular endothelium and syncytiotrophoblasts.** A novel placenta-derived soluble form of Eng, referred to as soluble endoglin (sEng), is an anti-angiogenic protein that appears to be another important mediator of preeclampsia.
- Although the precise relationship of sEng to sFlt-1 is unknown, it appears that both sEng and sFlt-1 contribute to the pathogenesis of the maternal syndrome through separate mechanisms. Several lines of evidence support this hypothesis
- **Circulating syncytiotrophoblast debris** — Circulating syncytiotrophoblast debris have been hypothesized to contribute to maternal inflammation and some of the features of the maternal syndrome.

- Signs of maternal inflammation which appear to be present in normal pregnancies at term are exaggerated in preeclampsia. Trophoblastic debris and the microparticles shed during normal pregnancy are proinflammatory and this process is amplified in preeclampsia. It is likely that the inflammatory state may increase the vascular endothelial sensitivity to toxic factors such as sFlt1 and sEng, although definitive evidence is lacking

Diagnosis

- ⊕ Preeclampsia is a clinical syndrome that embraces a wide spectrum of signs and symptoms that have been clinically observed to develop alone or in combination. Elevated BP is the traditional hallmark for diagnosis of the disease. However, recent evidence suggests that in some patients, the disease may manifest itself in the form of either a capillary leak (ascites, proteinuria) or a spectrum of abnormal hemostasis with multiple organ dysfunction. These latter patients usually present with clinical manifestations that are not typical of preeclampsia (i.e., hypertension is absent).
- ⊕ The diagnosis of preeclampsia and the severity of the disease process are generally based on maternal BP. There are many factors that may influence measurement of BP with a sphygmomanometer, including the accuracy of the equipment used, size of the cuff, duration of the rest period before recording, the posture of the patient, and the Korotkoff phase used (phase IV or phase V for diastolic BP measurement).
- ⊕ Steer recommends that all BP values be recorded with the woman in a sitting position for ambulatory patients or in a semi-reclining position for hospitalized patients. The right arm should be used consistently, with the arm being in a roughly horizontal position at heart level. For diastolic BP measurements, both phases (muffling sound and disappearance sound) should be recorded. This is very important, because the level measured at phase IV is about 5 to 10 mm Hg higher than that measured at phase V.
- ⊕ Overall, pregnancy outcomes were similar among women who remained normotensive and those who demonstrated a rise in diastolic pressure of 15 mm Hg or higher but did not reach 90 mm Hg. The use of an increase in BP as a diagnostic criterion is principally influenced by two factors: gestational age at time of first observation and frequency of BP measurements. Thus, these criteria are unreliable to diagnose preeclampsia as such.
- ⊕ The diagnosis of preeclampsia requires the presence of an elevated BP with proteinuria. The presence of proteinuria is usually determined by the use of either dipstick or protein/creatinine ratio in random urine samples. The concentration of urinary protein is highly variable. It is influenced by several factors, including contamination, urine specific gravity, pH, exercise, and posture. In addition, urinary protein/creatinine excretion is highly variable in patients with preeclampsia. Moreover, urinary dipstick determinations as well as total protein-to-creatinine ratio correlate poorly with the amount of proteinuria found in 24-hour urine determinations in women with gestational hypertension.

- ⊕ Therefore, the definitive test for diagnosing proteinuria should be quantitative measurement of total protein excretion over a 24-hour period. The diagnosis of severe preeclampsia requires that proteinuria of more than 5 g/24 h be documented. Using urine dipstick measurements ($\geq 3+$) is not adequate.
- ⊕ The traditional criteria to confirm a diagnosis of preeclampsia (new onset of hypertension and proteinuria after 20 weeks' gestation) are appropriate to use in the majority of healthy nulliparous women. However, in some women, the development of severe gestational hypertension (without proteinuria) is associated with higher maternal and perinatal morbidities than in women with mild preeclampsia.
- ⊕ In addition, hypertension or proteinuria may be absent in 10 to 15 percent of women who develop the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome), and in 20 to 25 percent of those who develop eclampsia

Prediction of Preeclampsia

- ⊕ A review of the world literature reveals that more than 100 clinical, biophysical and biochemical tests have been recommended to predict or identify the patient at risk for the future development of the disease. The results of the pooled data for the various tests and the lack of agreement between serial tests suggest that none of these clinical tests is sufficiently reliable for use as a screening test in clinical practice.
- ⊕ Numerous biochemical markers have been proposed to predict which women are destined to develop preeclampsia. These biochemical markers were generally chosen on the basis of specific pathophysiologic abnormalities that have been reported in association with preeclampsia. Thus, these markers have included:
 - ❖ Markers of placental dysfunction,
 - ❖ Endothelial and coagulation activation,
 - ❖ Angiogenesis, and
 - ❖ Markers of systemic inflammation.
- ⊕ However, the results of various studies evaluating the reliability of these markers in predicting preeclampsia have been inconsistent, and many of these markers suffer from poor specificity and predictive values for routine use in clinical practice. [80] [81] [82] [83]
- ⊕ **Doppler ultrasound** is a useful method to assess uterine artery blood flow velocity in the second trimester. An abnormal uterine artery velocity wave form is characterized by a high resistance index or by the presence of an early diastolic notch (unilateral or bilateral). Pregnancies complicated by abnormal uterine artery Doppler findings in the second trimester are associated with more than six-fold increase in rate of preeclampsia. However, the sensitivity of an abnormal uterine artery Doppler for predicting preeclampsia ranges from 20 to 60 percent, with a positive predictive value of 6 to 40 percent.
- ⊕ Current data do not support this test for routine screening of pregnant women for preeclampsia, but uterine artery Doppler could be beneficial as a screening test in women at very high risk for preeclampsia if an effective preventive treatment becomes available

Prevention of Preeclampsia

- ⊕ There are numerous clinical trials describing the use of various methods to prevent or reduce the incidence of preeclampsia. Because the etiology of the disease is unknown, these interventions have been used in an attempt to correct theoretical abnormalities in preeclampsia. A detailed review of these trials is beyond the scope of this chapter; however, the results of these studies have been the subject of several recent systemic reviews.
- ⊕ In short, randomized trials have evaluated protein or salt restriction, zinc, magnesium, fish oil, or vitamins C and E supplementation, the use of diuretics and other antihypertensive agents, as well as heparin to prevent preeclampsia in women with various risk factors. These trials have had limited sample size, and results have revealed minimal to no benefit. There is some suggestion from observational studies that heparin reduces recurrent preeclampsia in women with thrombophilias. Some of the methods used are summarized in the box, "Methods Used to Prevent Preeclampsia."

Calcium Supplementation

- ⊕ The relationship between dietary calcium intake and hypertension has been the subject of several experimental and observational studies. Epidemiologic studies have documented an inverse association between calcium intake and maternal BP, and the incidences of preeclampsia and eclampsia. The BP-lowering effect of calcium is thought to be mediated by alterations in plasma renin activity and parathyroid hormone. In addition, calcium supplementation during pregnancy has been shown to reduce vascular sensitivity to angiotensin II
- ⊕ In the Cochrane review, calcium supplementation was associated with reduced hypertension; reduced preeclampsia, particularly for those at high risk and with low baseline dietary calcium intake (for those with adequate calcium intake, the difference was not statistically significant). No side effects of calcium supplementation have been recorded in the trials reviewed. However, the reduction was not reflected in any overall reduction in stillbirths or neonatal death. In the largest trial to date, of 4,589 women in developed countries, no reduction in the rate of preeclampsia or severity of preeclampsia or in timing of its onset was observed with calcium supplementation.
- ⊕ At present, the benefit of calcium supplementation for preeclampsia prevention in women with low dietary calcium intake remains unclear

Antithrombic Agents

- ⊕ Preeclampsia is associated with vasospasm and activation of the coagulation-hemostasis systems. Enhanced platelet activation plays a central role in the above-mentioned process and reflects abnormalities in the thromboxane/prostacyclin balance. Hence, several authors have used pharmacologic manipulation to alter the above-mentioned ratio in an attempt to prevent or ameliorate the course of preeclampsia.

- ⊕ Aspirin inhibits the synthesis of prostaglandins by irreversibly acetylating and inactivating cyclooxygenase. In vitro, platelet cyclooxygenase is more sensitive to inhibition by low doses of aspirin (<80 mg) than vascular endothelial cyclooxygenase. This biochemical selectivity of low-dose aspirin appears to be related to its unusual kinetics that result in presystemic acetylation of platelets exposed to higher concentrations of aspirin in the portal circulation.
- ⊕ The majority of randomized trials for the prevention of preeclampsia have used low-doses of aspirin (50 to 150 mg/dl). The rationale for recommending low-dose aspirin prophylaxis is the theory that the vasospasm and coagulation abnormalities in preeclampsia are caused partly by an imbalance in the thromboxane A₂-to-prostacyclin ratio
- ⊕ The reviewers concluded that antiplatelet agents, largely low-dose aspirin, have small to moderate benefits when used for prevention of preeclampsia. Low-dose aspirin was also found to be safe. However, more information is clearly required to assess which women are most likely to benefit from this therapy as well as when treatment is optimally started, and what dose to use.
- ⊕ Some authors recommend that aspirin use should be based on individualized risk assessment for preeclampsia. However, the available data do not support such a recommendation.

Vitamin C and E

- ⊕ One recent study has suggested a beneficial effect from pharmacologic doses of vitamins E and C in women identified as being at-risk for preeclampsia by means of abnormal uterine Doppler flow velocimetry. However, the study had limited sample size and must be confirmed in other populations. In contrast, another randomized trial with limited sample size in women at very high risk for preeclampsia found no reduction in the rate of preeclampsia with vitamin C and E supplementation.
- ⊕ Finally, it is important to emphasize that most of the positive trials found a benefit in the prevention of preeclampsia as defined, but not in pregnancy outcome.

Laboratory Abnormalities in Preeclampsia

1. Renal Function

- ◆ Renal plasma flow and glomerular filtration rate (GFR) increase during normal pregnancy. These changes are responsible for a fall in serum creatinine, urea, and uric acid concentrations. In preeclampsia, vasospasm and glomerular capillary endothelial swelling (glomerular endotheliosis) lead to an average reduction in **GFR of 25 percent below** the rate for normal pregnancy.
- ◆ Serum creatinine is rarely elevated in preeclampsia, but uric acid is commonly increased.
- ◆ The clinical significance of elevated uric acid levels in preeclampsia/eclampsia has been confusing. Hyperuricemia is associated with renal dysfunction, especially decreased renal **tubular secretion**, and has been consistently associated with **glomerular endotheliosis**. In addition, it has been linked with increased oxidative stress in preeclampsia. Despite the fact that uric acid levels are elevated in women with preeclampsia; this test is not sensitive or specific for the diagnosis of preeclampsia.
- ◆ Elevated uric acid levels above **6 mg/dl** are often found in women with normotensive multifetal pregnancies. As a result, some authors suggested that to secure a diagnosis of preeclampsia based upon elevated uric acid values, the upper limit should be adjusted for those with multiple gestations. Elevated uric acid values are also found in women with acute fatty liver of pregnancy and underlying renal disease. **It is suggested that uric acid values not be used as an indication for delivery in women with preeclampsia**

2. Hepatic Function

- The liver is not primarily involved in preeclampsia, and hepatic involvement is observed in only **10 percent of women with severe preeclampsia**.
- Fibrin deposition has been found along the walls of hepatic sinusoids in preeclamptic patients with no laboratory or histologic evidence of liver involvement.
- When liver dysfunction does occur in preeclampsia, mild elevation of serum transaminase is most common. Bilirubin is rarely increased in preeclampsia, but when elevated, **the indirect fraction predominates**. Elevated liver enzymes are part of the of HELLP syndrome, a variant of severe preeclampsia.

3. Hematologic Changes

- Many studies have evaluated the hematologic abnormalities in women with preeclampsia. Plasma fibrinopeptide-A, D-dimer levels, and circulating thrombin-antithrombin complexes are higher in women with preeclampsia than in normotensive gravidas. **In contrast, plasma antithrombin III activity is decreased**. These findings indicate enhanced thrombin generation.

- Plasma fibrinogen rises progressively during normal pregnancy. When a group of 50 severe preeclamptic women were compared with 50 normotensive women matched by gestational age, no differences in mean plasma fibrinogen levels were found between the two groups. In general, plasma fibrinogen levels are rarely reduced in women with preeclampsia in the absence of abruptio placentae.
- Thrombocytopenia is the most common hematologic abnormality in women with preeclampsia. It is correlated with the severity of the disease process and the presence or absence of abruptio placentae. A platelet count of less than 150,000/mm³ has been reported in 32 to 50 percent of women with severe preeclampsia
- Leduc and associates studied the coagulation profile (platelet count, fibrinogen, prothrombin time, and partial thromboplastin time) in 100 consecutive women with severe preeclampsia. A platelet count less than 150,000/mm³ was found in 50 percent and a count of less than 100,000/mm³ in 36 percent of the women. Thirteen women had a fibrinogen level of less than 300 mg/dl, and two had prolonged prothrombin and partial thromboplastin times, as well as thrombocytopenia on admission. They found the admission platelet count to be an excellent predictor of subsequent thrombocytopenia, and concluded that fibrinogen levels, prothrombin time, and partial thromboplastin time should be obtained only in women with a platelet count of less than 100,000/mm³.

The HELLP Syndrome

- ☀ Recent reports have described the HELLP syndrome in severe preeclampsia. There is considerable debate regarding the definition, diagnosis, incidence, etiology, and management of this syndrome. Patients with such findings were previously described by many investigators. Weinstein considered it a unique variant of preeclampsia and coined the term HELLP syndrome for this entity, whereas MacKenna and colleague considered it to be misdiagnosed preeclampsia. Barton and associates performed liver biopsies in patients with preeclampsia and HELLP syndrome. Periportal necrosis and hemorrhage were the most common histopathologic findings. In addition, they found that the extent of the laboratory abnormalities in HELLP syndrome including the platelet count and liver enzymes did not correlate with hepatic histopathologic findings.

Clinical Findings

- ☀ The reported incidence of HELLP syndrome in preeclampsia has been variable, reflecting the differences in diagnostic criteria. The syndrome appears to be more common in white women and is also higher in preeclamptic patients who have been managed conservatively.
- ☀ Early detection of HELLP syndrome can be a challenge in that many women present with nonspecific symptoms or subtle signs of preeclampsia.
- ☀ The various signs and symptoms reported are not diagnostic of preeclampsia and may also be found in women with severe preeclampsia-eclampsia without HELLP syndrome.

- ☀ **Right upper quadrant** or epigastric pain and nausea or vomiting has been reported with a frequency ranging from 30 to 90 percent.
- ☀ Most patients give a history of malaise for several days before presentation, and some have a nonspecific viral-like syndrome, which led one investigator to suggest performing laboratory investigations (completed blood count and liver enzymes) in all pregnant women with suspected preeclampsia having these symptoms during the third trimester.
- ☀ Headaches are reported by 33 to 61 percent of the patients, whereas visual changes are reported in approximately 17 percent.
- ☀ A small subset of patients with HELLP syndrome may present with symptoms related to thrombocytopenia, such as bleeding from mucosal surfaces, hematuria, petechial hemorrhages, or ecchymosis
- ☀ Occasionally, the presence of this syndrome is associated with hypoglycemia, leading to coma, severe hyponatremia, and cortical blindness. **A rare but interesting complication of HELLP syndrome is transient nephrogenic diabetes insipidus.** Unlike central diabetes insipidus, which occurs due to the diminished or absent secretion of arginine vasopressin by the hypothalamus, transient nephrogenic diabetes insipidus is characterized by a resistance to arginine vasopressin mediated by excessive vasopressinase. It is postulated that elevated circulating vasopressinase may result from impaired hepatic metabolism of the enzyme.
- ☀ Although the majority of patients have hypertension (82 to 88 percent), it may be only mild in 15 to 50 percent of the cases, and absent in 12 to 18 percent. The majority of the patients (86 to 100 percent) have proteinuria by dipstick examination. However, it has been reported to be absent in 13 percent of cases.

Management of HELLP Syndrome

- ☀ Management of preeclamptic patients presenting with the HELLP syndrome is highly controversial. Consequently, there are several therapeutic modalities described in the literature to treat or reverse the HELLP syndrome. Most of these modalities are similar to those used in the management of severe preeclampsia remote from term
- ☀ The results of the above-mentioned studies suggest **that expectant management is possible in a very select group of patients with alleged HELLP syndrome before 34 weeks' gestation.** However, despite pregnancy prolongation in some of these cases, the overall perinatal outcome was not improved compared with cases at a similar gestational age who were delivered within 48 hours after the diagnosis of HELLP syndrome.

Maternal and Perinatal Outcome

- ☀ The presence of HELLP syndrome is associated with an increased risk of maternal death (1 percent) and **increased rates of maternal morbidities such as pulmonary edema (8 percent), acute renal failure (3 percent), DIC (15 percent), [144] abruptio placentae (9 percent), liver hemorrhage or failure (1 percent), adult respiratory distress syndrome (ARDS), sepsis, and stroke (<1 percent).**

- ☀ Pregnancies complicated by HELLP syndrome are also associated with increased rates of wound hematomas and the need for transfusion of blood and blood products. The rate of these complications depends on the population studied, the laboratory criteria used to establish the diagnosis, and on the presence of associated preexisting medical conditions (chronic hypertension, lupus), or obstetric complications (abruptio placentae, peripartum hemorrhage, fetal demise, eclampsia). The development of HELLP syndrome in the postpartum period also increases the risk of renal failure and pulmonary edema.
- ☀ The presence of abruptio placentae increases the risk of DIC, need for blood transfusions, pulmonary edema, and renal failure. Patients who have large volume of ascites appear to have a high rate of cardiopulmonary complications. Finally, women who meet all the criteria suggested for diagnosis will have higher rates of maternal complications than those who have partial HELLP or elevated liver enzymes only
- ☀ The HELLP syndrome may develop antepartum or postpartum. Analysis of 442 cases studied by Sibai and associates revealed that 309 (70 percent) had evidence of the syndrome antepartum, and 133 (30 percent) developed the manifestations postpartum. There were four maternal deaths, and morbidity was frequent
- ☀ In the postpartum period, the time of onset of the manifestations may range from a few hours to 7 days, the majority developing within 48 hours postpartum. Thus, laboratory assessment for potential HELLP syndrome should be considered during the first 48 hours postpartum in women with significant hypertension or symptoms of severe preeclampsia. Eighty percent of the women who develop HELLP syndrome postpartum have had preeclampsia before delivery, whereas 20 percent had no evidence of either preeclampsia either antepartum or intrapartum. It is the author's experience that patients in this group are at increased risk for the development of pulmonary edema and acute renal failure. The differential diagnosis should include exacerbation of systemic lupus erythematosus, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome.

Recommended Management

- ☀ The clinical course of women with HELLP syndrome is usually characterized by progressive and sometimes sudden deterioration in maternal and fetal condition. Therefore, patients with a suspected diagnosis of HELLP syndrome should be hospitalized immediately and observed in a labor and delivery unit.
- ☀ Such patients should be managed as if they had severe preeclampsia and should initially receive intravenous magnesium sulfate as prophylaxis against convulsions and antihypertensive medications to keep systolic BP below 160 mmHg or diastolic BP below 105 mm Hg. This can be achieved with a 5-mg bolus dose of hydralazine, to be repeated as needed every 15 to 20 minutes for a maximum dose of 20 mg per hour. BP is recorded every 15 minutes during therapy and every hour once the desired values are achieved. If hydralazine does not lower BP adequately or if maternal side effects such as tachycardia or headaches develop, another drug such as labetalol or Nifedipine can be used.



- ☀ The recommended dose of labetalol is 20 to 40 mg IV every 10–15 minutes for a maximum of 220 mg, and the dose of nifedipine is 10 to 20 mg orally every 30 minutes for a maximum dose of 50 mg. During the observation period, maternal and fetal conditions should be followed carefully.
- ☀ The recommended regimen of magnesium sulfate is a loading dose of 6 g given over 20 minutes, followed by a maintenance dose of 2 g per hour as a continuous intravenous solution. Magnesium sulfate is initiated at the beginning of the observation period and then continued during labor and for at least 24 hours postpartum.
- ☀ Once the diagnosis of HELLP syndrome is confirmed, a decision must be made regarding the need for delivery. Women with HELLP syndrome who are less than 35 weeks' gestation should be referred to a tertiary care facility if maternal condition is stable. The first priority is to assess and stabilize the maternal condition, particularly BP and coagulation abnormalities. The next step is to evaluate fetal status with the use of fetal heart rate monitoring, biophysical profile, or Doppler assessment of fetal vessels. Finally, a decision must be made as to whether delivery should be initiated or delivery could be delayed for 48 hours to allow the full benefit of corticosteroids.
- ☀ Thus, in practice, delivery is undertaken in all patients with true HELLP syndrome except in those with a gestational age between 24 to 34 weeks with stable maternal and fetal conditions. These latter patients are given betamethasone and are generally then delivered within 24 hours after the last dose of corticosteroids. Maternal and fetal conditions are assessed continuously during this time period. In some of these patients, there may be transient improvement in maternal laboratory tests. However, delivery is still recommended despite such improvement.

Intrapartum Management

- ☀ The presence of HELLP syndrome is not an indication for immediate cesarean delivery. Such an approach might prove detrimental for both mother and fetus. The decision to perform a cesarean delivery should be based on gestational age, fetal condition, the presence of labor, and the cervical Bishop score.
- ☀ Elective cesarean delivery is recommended for all women with HELLP syndrome below 30 weeks' gestation not in labor and with a Bishop score less than five. Elective cesarean delivery is also undertaken for those with HELLP syndrome complicated by fetal growth restriction or oligohydramnios, particularly if the gestational age is below 32 weeks in the presence of an unfavorable cervical Bishop score.
- ☀ Patients having labor or rupture of membranes are allowed to deliver vaginally in the absence of obstetric complications. When induction is indicated, it is initiated with either oxytocin infusion or prostaglandins in patients with a gestational age at above 30 weeks, irrespective of the amount of cervical dilatation or effacement. A similar approach is used for those at ≤ 30 weeks if the cervical Bishop score is at least five.

- ☀ Maternal pain relief during labor and delivery can be provided by intermittent use of small doses of systemic opioids. Local infiltration anesthesia can be used for all vaginal deliveries if an episiotomy or repair of a laceration is necessary. The use of a pudendal block is contraindicated in these patients because of the risk of bleeding and hematoma formation into this area.
- ☀ Epidural anesthesia is also contraindicated particularly if the platelet count is less than 75,000/mm³. Therefore, general anesthesia is the method of choice for cesarean delivery in such patients.

Indications and Management during Cesarean Delivery in HELLP Syndrome

Indications for cesarean delivery

Nonreassuring fetal status

Abnormal fetal presentation

<30 weeks and Bishop score <5

<32 weeks with IUGR or oligohydramnios and Bishop score <5

Known subcapsular liver hematoma

Suspected abruptio placentae

Management during cesarean delivery

General anesthesia for platelet count <75,000/mm³

Transfuse 6 units of platelets if count <40,000/mm³

Insert subfascial drain

Secondary skin closure or leave subcutaneous drain

Observe for bleeding from upper abdomen before closure

- ☀ Platelet transfusions are indicated either before or after delivery in all patients with HELLP syndrome in the presence of significant bleeding (ecchymosis, bleeding from gums, oozing from puncture sites, wound, intraperitoneal, and so on), and in all those with a platelet count of less than 20,000/mm³. However, repeated platelet transfusions are not necessary because of the short half life of the transfused platelets in such patients. Correction of thrombocytopenia is also important before any surgery.
- ☀ Administration of 6 units of platelets is recommended in all patients with a platelet count less than 40,000/mm³ before intubation if cesarean delivery is needed. Generalized oozing from the incision site can occur during surgery or in the immediate postpartum period because of the continued drop in platelet count in some of these patients. The risk of hematoma formation at these sites is approximately 20 percent. Some individuals prefer to use a vertical skin incision, whereas others employ a subfascial drain and keep the skin incision open for at least 48 hours in patients requiring cesarean delivery

☀ Postpartum Management

- ☀ Following delivery, patients with HELLP syndrome should receive close monitoring of vital signs, fluid intake and output, laboratory values, and pulse oximetry for at least 48 hours. Intravenous magnesium sulfate prophylaxis is generally continued for 48 hours, and antihypertensive drugs are employed if the systolic BP is at least 155 mm Hg or if the diastolic BP is at least 105 mm Hg. In general, the majority of patients will show evidence of resolution of the disease process within 48 hours after delivery. However, some patients, especially those with abruptio placentae plus DIC, those with severe thrombocytopenia (platelet count <20,000/mm³), and those with severe ascites or significant renal dysfunction may show delayed resolution or even deterioration in their clinical condition.
- ☀ Such patients are at risk for the development of pulmonary edema from transfusion of blood and blood products, fluid mobilization, and compromised renal function. These patients are also at risk for acute tubular necrosis and may need dialysis and require intensive monitoring for several days. Some authors have suggested that such patients might benefit from plasmapheresis or plasma transfusions. In practice, most of these patients will recover with supportive therapy only.
- ☀ The clinical and laboratory findings of HELLP syndrome may develop for the first time in the postpartum period. In these patients, the time of onset of the manifestations ranges from a few hours to 7 days, with the majority developing within 48 hours postpartum. Hence, all postpartum women and their health care providers should be educated and be aware of the signs and symptoms of HELLP syndrome. Management of patients with postpartum HELLP syndrome should be similar to that in the antepartum period, including the use of magnesium sulfate.

Subcapsular Hematoma of the Liver in HELLP Syndrome

- ☀ Because it occurs so rarely, the diagnosis of a subcapsular hematoma of the liver in pregnancy is often overlooked. Indeed, in four cases described from the University of Tennessee, the initial clinical impression was placental abruption with DIC in three cases and a complication of a postpartum tubal ligation in the fourth patient. The differential diagnosis of an unruptured subcapsular hematoma of the liver in pregnancy should include acute fatty liver of pregnancy, ruptured uterus, placental abruption with DIC, and TTP. Most patients present in the third or late second trimester of pregnancy, although cases have been reported in the immediate postpartum period. In addition to the signs and symptoms of preeclampsia, physical findings consistent with peritoneal irritation and hepatomegaly may be present. Profound hypovolemic shock with hypotension in a previously hypertensive patient is a hallmark of rupture of the hematoma.
- ☀ Laboratory evaluation is often consistent with DIC, including low platelet count, low fibrinogen, and prolonged prothrombin and partial thromboplastin times. As a result of hemolysis, total bilirubin and serum lactate dehydrogenase are markedly elevated. Other liver function tests such as AST and ALT are also significantly elevated.
- ☀ Rupture of a subcapsular hematoma of the liver is a life-threatening complication of HELLP syndrome. In most instances, rupture involves the right lobe and is preceded by the development of a parenchymal hematoma.

- ☀ The condition usually presents with severe epigastric pain that may persist for several hours before circulatory collapse. Patients frequently present with shoulder pain, shock, or evidence of massive ascites, respiratory difficulty, or pleural effusions, and often with a dead fetus. An ultrasound, computed axial tomographic (CAT) scan, or magnetic resonance imaging (MRI) of the liver should be performed to rule out subcapsular hematoma and detect the presence of intraperitoneal bleeding. Paracentesis can confirm intraperitoneal hemorrhage suspected by radiographic imaging
- ☀ The presence of a ruptured subcapsular liver hematoma resulting in shock is a surgical emergency requiring acute multidisciplinary treatment.[163] Resuscitation should consist of massive transfusions of blood, correction of the coagulopathy with fresh frozen plasma and platelets, and immediate laparotomy. Options at laparotomy include packing and drainage, the preferred approach, surgical ligation of the hemorrhaging hepatic segments, embolization of the hepatic artery to the involved liver segment, and loosely suturing omentum or surgical mesh to the liver to improve integrity. Even with appropriate treatment, maternal and fetal mortality is over 50 percent.
- ☀ Mortality is most commonly associated with exsanguination and coagulopathy. Initial survivors are at increased risk for developing ARDS, pulmonary edema, and acute renal failure in the postoperative period.
- ☀ Surgical repair has been recommended for hepatic hemorrhage without liver rupture. More recent experience suggests, however, that this complication may be preferably managed conservatively in patients who remain hemodynamically stable.
- ☀ Management should include close monitoring of hemodynamics and coagulation status. Serial assessment of the subcapsular hematoma with ultrasound or computed tomographic (CT) scan is necessary with immediate intervention for rupture or worsening maternal status. It is important with conservative management to avoid exogenous sources of trauma to the liver such as abdominal palpation, convulsions, or emesis and to use care in transportation of the patient. Indeed, any sudden increase in intraabdominal pressure could potentially lead to rupture of the subcapsular hematoma.
- ☀ Stable patient with an unruptured subcapsular hematoma may be managed conservatively. Constant monitoring must continue during this management, however, because patients can rapidly become unstable following rupture of the hematoma.
- ☀ Survival depends on rapid diagnosis and medical and surgical stabilization. The coagulopathy must be aggressively reversed, because failure to do so is associated with an increased incidence of renal failure. In addition, these patients should be managed in an intensive care unit with close hemodynamic monitoring to avoid pulmonary edema, and respiratory compromise. Postpartum follow-up for patients with subcapsular hematoma of the liver should include serial imaging studies until the defect resolves

Hemodynamic Monitoring in Preeclampsia

- ☀ The true hemodynamic findings in patients with preeclampsia are controversial. A review of the English literature demonstrates considerable disagreement regarding one or more of the hemodynamic parameters studied.

- ☀ The findings suggest that **cardiac index and PCWP are either low or normal in severe preeclampsia**. The reported CVP values also ranged from 2 to 6 mm Hg.
- ☀ In summary, the true hemodynamic findings of preeclampsia remain unknown. Moreover, the clinical utility of invasive hemodynamic monitoring in preeclampsia is debatable. The majority of the invasive monitoring data indicate that both cardiac output and systemic vascular resistance appear to be elevated in women with severe preeclampsia.
- ☀ **This finding suggests that the problem in preeclampsia is a systemic vascular resistance that is inappropriately high for the level of cardiac output.** Both the PCWP and the CVP appear to be in the low to normal range; however, there is no correlation between the two values.

Antepartum Management of Mild Hypertension-Preeclampsia

Gestational Hypertension

- Results of several randomized trials reveal that control of maternal BP with antihypertensive **drugs does not improve pregnancy outcome in women with gestational hypertension**
- Women with gestational hypertension are at risk for progression to either severe hypertension, preeclampsia, or eclampsia. The risks are increased with a lower gestational age at the time of diagnosis. Therefore, these patients require close observation of maternal and fetal conditions.
- Maternal evaluations require weekly prenatal **visits, education about reporting preeclamptic symptoms, evaluation of complete blood count, platelet count, and liver enzymes.** Fetal evaluation includes ultrasound examination of fluid and estimated fetal weight at the time of diagnosis and weekly nonstress testing. Restriction of dietary salt as well as physical activity has not proven beneficial in the management of these patients
- In the absence of progression to severe hypertension or preeclampsia, women with gestational hypertension can continue pregnancy until term. During labor and immediately postpartum, they do not require seizure prophylaxis because the rate of eclampsia in these women is less than 1 in 500.
- The optimal management of women with **mild gestational hypertension or preeclampsia before 37 weeks' gestation is controversial.** There is disagreement regarding the benefits of hospitalization, complete bed rest and use of antihypertensive medications.

Recommended Management

- The primary objective of management in women with gestational hypertension-preeclampsia must always be safety of the mother and then delivery of a mature newborn that will not require intensive and prolonged neonatal care. This objective can be achieved by formulating a management plan that takes into consideration one or more of the following: the severity of the disease process, fetal gestational age, maternal and fetal status at time of initial evaluation, presence of labor, cervical Bishop score, and the wishes of the mother.

Mild Hypertension or Preeclampsia

- Once the diagnosis of mild gestational hypertension or mild preeclampsia is made, subsequent therapy will depend on the results of maternal and fetal evaluation. In general, women with mild disease developing at 37 weeks' gestation or later have pregnancy outcomes similar to those found in normotensive pregnancies. Thus, at or near term in women with a favorable cervix and in those patients who are considered noncompliant, induction of labor is recommended. In addition, cervical ripening with prostaglandins and induction of labor can be used in women with mild preeclampsia and an unfavorable cervix at 37 weeks or later because of the slight increased risk for development of abruptio placentae and progression to severe disease.
- In women who remain undelivered, close maternal and fetal evaluation are essential. These women are instructed to eat a regular diet with no salt restriction, and to restrict their activity but not to complete bed rest. Diuretics or antihypertensive medication are not used because of the potential to mask the diagnosis of severe disease.
- In addition, the current data suggest that antihypertensive therapy in women with mild gestational hypertension or preeclampsia does not improve perinatal outcome. At the time of initial and subsequent visits, the women are educated and instructed about reporting symptoms of severe preeclampsia. They are also advised to come to the hospital or outpatient facility immediately if they develop abdominal pain, uterine contractions, vaginal spotting, or decreased fetal movement.
- In women with mild gestational hypertension, fetal evaluation should include a non-stress test (NST) and an ultrasound examination of estimated fetal weight and amniotic fluid index. If the results are normal, then no repeat testing is undertaken as previously described.
- Maternal evaluation includes measurements of hematocrit, platelet count, liver function tests, and a 24-hour urine protein once weekly. The women are usually seen twice a week for evaluation of maternal BP, urine protein by dipstick, and symptoms of impending eclampsia. This evaluation is extremely important for early detection of progression to preeclampsia or severe hypertension. The onset of maternal symptoms or a sudden increase in BP to severe values or development of proteinuria ($\geq 2+$ on dipstick) requires prompt hospitalization for close evaluation.
- In women with mild preeclampsia at less than 37 weeks' gestation but at > 32 weeks, outpatient management can be considered in those with systolic BP at ≤ 150 mmHg and/or diastolic BP at ≤ 100 mmHg and a urine protein of ≤ 1000 mg/24 hours if they have no symptoms and if they have normal liver enzymes and a normal platelet count ($> 100,000/\text{mm}^3$).

- Women who do not satisfy these criteria are hospitalized, particularly those with mild preeclampsia before 32 weeks. During ambulatory management, women are instructed to rest at home and perform BP measurements and urine dipstick daily, and are given instructions about prompt reporting of symptoms of severe disease. These women are then seen twice weekly, at which time a platelet count and liver enzymes are performed. Fetal evaluation includes daily fetal movement count, NST, and serial ultrasound evaluation of fetal growth and amniotic fluid. If there is evidence of disease progression (significant increase in BP or proteinuria to levels above the threshold mentioned previously or if they have new onset of symptoms or if there is evidence of abnormal blood tests or abnormal fetal growth), these women are then hospitalized for the duration of pregnancy. Women managed in the hospital receive similar maternal and fetal evaluation.

Expectant Management of Severe Preeclampsia

- The clinical course of severe preeclampsia may be characterized by progressive deterioration in both maternal and fetal conditions. Because these pregnancies have been associated with increased rates of maternal morbidity and mortality and with significant risks for the fetus (growth restriction, hypoxemia, and death), there is universal agreement that all such patients should be delivered if the disease develops after 34 weeks' gestation. Prompt delivery is also clearly indicated when there is imminent eclampsia (persistent severe symptoms), multiorgan dysfunction, severe IUGR (<5th percentile), suspected abruptio placentae, or nonreassuring fetal testing before 34 weeks' gestation.
- There is disagreement about management of patients with severe preeclampsia before 34 weeks' gestation when the maternal condition is stable and fetal condition is reassuring. In such patients, some authors consider delivery as the definitive treatment regardless of gestational age, whereas others recommend prolonging pregnancy until development of maternal or fetal indications for delivery or until achievement of fetal lung maturity or 34 weeks' gestation.
- Although delivery is always appropriate for the mother, it may not be optimal for the fetus that is extremely premature. In the past, it was believed that infants born prematurely to severely preeclamptic women had lower rates of neonatal mortality and morbidity as compared with infants of similar gestational age born to non preeclamptic women.
- This belief was based on the clinical impression that fetuses of preeclamptic women have accelerated lung and neurologic maturation as a result of stress in utero. This phenomenon, however, has never been documented in case-control studies.[182] In contrast, several recent case-control investigations have demonstrated that premature infants born after severe preeclampsia have similar neonatal complications and mortality and have higher rates of admission to neonatal intensive care units as compared with other premature infants of similar gestational age. In addition, the results of case-controlled studies reveal that fetuses of preeclamptic women do not exhibit accelerated lung or neurologic maturation.

- During expectant management, patients should be aware that the decision to continue such management will be made on a daily basis and that the median days of pregnancy prolongation is 7 days (range, 2 to 35 days). It is important to mention that there are only two randomized trials (133 women) that compared a policy of early elective delivery with a policy of delayed delivery. Nevertheless, the results of retrospective and observational studies (more than 700 women) suggest that expectant management is associated with reduced short-term neonatal morbidity
- In the past, there was uncertainty regarding the efficacy and safety of corticosteroids in women with severe preeclampsia before 34 weeks' gestation. A prospective double-blind randomized trial of 218 women with severe preeclampsia with a gestational age between 26 and 34 weeks receiving either betamethasone (n = 110) or placebo (n = 108) reported a significant reduction in the rate of respiratory distress syndrome (RR, 0.53; 95 percent CI, 0.35 to 0.82) in the steroids group.[154] Corticosteroids use also was associated with a reduction in the risks of neonatal intraventricular hemorrhage (RR, 0.35; 95 percent CI, 0.15 to 0.86), neonatal infection (RR, 0.39; 95 percent CI, 0.39 to 0.97), and neonatal death (RR, 0.5; 95 percent CI, 0.28 to 0.89). However, there were no differences in maternal complications between the two groups. Thus, the data support the use of steroids to reduce neonatal complications in women with severe preeclampsia at 34 weeks' gestation or less

Severe Preeclampsia

- The presence of severe disease mandates immediate hospitalization in labor and delivery. Intravenous magnesium sulfate is begun to prevent convulsions, and antihypertensive medications are administered to lower severe levels of hypertension (systolic pressure ≥ 160 mm Hg and/or diastolic pressure ≥ 110 mm Hg). The aim of antihypertensive therapy is to keep systolic pressure between 140 and 155 mm Hg and diastolic pressure between 90 and 105 mm Hg. During the observation period, maternal and fetal conditions are assessed, and a decision is made regarding the need for delivery.
- Those with a gestational age at 24 to 34 weeks are given corticosteroids to accelerate fetal lung maturity. Maternal evaluation includes monitoring of BP, urine output, cerebral status, and the presence of epigastric pain, tenderness, labor or vaginal bleeding. Laboratory evaluation includes a platelet count, liver enzymes, and serum creatinine. Fetal evaluation includes continuous fetal heart monitoring, a biophysical profile, and ultrasonographic assessment of fetal growth and amniotic fluid. Patients with resistant severe hypertension despite maximum doses of intravenous labetalol (220 mg) plus oral nifedipine (50 mg) or persistent cerebral symptoms while on magnesium sulfate are delivered within 24 to 48 hours irrespective of fetal gestational age. In addition, patients with either thrombocytopenia (platelet count $<100,000/\text{mm}^3$) or elevated liver enzymes with epigastric pain and tenderness, or with serum creatinine of 2.0 mg/dl or more are also delivered within 48 hours
- Women with a gestational age of 23 to 34 weeks are given corticosteroids and then delivered after 48 hours. Patients with a gestational age below 23 weeks are offered termination of pregnancy.

- Women at 23 to 32 weeks' gestation receive individualized management based on their clinical response during the 24-hour observation period. If BP is adequately controlled, and there is reassuring fetal assessment, magnesium sulfate is discontinued, and these women are then followed closely on the antepartum high-risk ward until 34 weeks' gestation or until development of a maternal or fetal indication for delivery. During hospitalization, they receive antihypertensive drugs, if needed, usually oral nifedipine (40 to 120 mg/day) plus labetalol (600 to 2400 mg/day), to keep systolic BP between 140 and 155 mm Hg and diastolic pressure between 90 and 105 mm Hg. Daily assessment of fetal well-being is also undertaken. In general, most patients will require delivery within 2 weeks, but some patients may continue their pregnancies for several weeks. It is important to emphasize that this therapy is appropriate only in a select group of patients and should be practiced in a tertiary care center with adequate maternal and neonatal intensive care facilities. Once the decision is made for delivery, the patients should receive magnesium sulfate in labor and for at least 24 hours postpartum.

Intrapartum Management

- The goals of management of women with gestational hypertension-preeclampsia are early detection of fetal heart rate abnormalities and progression from mild to severe disease, and the prevention of maternal complications. Pregnancies complicated by preeclampsia, particularly those with severe disease or fetal growth restriction, are at risk for reduced fetal reserve and abruptio placentae. Therefore, women with preeclampsia should receive continuous monitoring of fetal heart rate and uterine activity, with special attention to hyperstimulation and development of vaginal bleeding during labor. The presence of uterine irritability or recurrent fetal heart rate decelerations may be the first sign of abruptio placentae in these women.
- Some women with mild hypertension-preeclampsia progress to severe disease as a result of changes in cardiac output and stress hormones during labor. Therefore, women with gestational hypertension-preeclampsia should have BP recordings every hour and should be assessed for symptoms suggestive of severe disease. Those who develop severe hypertension or symptoms should be managed as patients with severe preeclampsia.
- Maternal pain relief during labor and delivery can be provided by either systemic opioids or segmental epidural anesthesia. Epidural analgesia is considered to be the preferred method of pain relief in women with mild gestational hypertension and mild preeclampsia. Although there is no unanimity of opinion regarding the use of epidural anesthesia in women with severe preeclampsia, a significant body of evidence indicates that epidural anesthesia is safe in these women. A randomized trial of 116 women with severe preeclampsia receiving either epidural analgesia or patient-controlled analgesia reported no differences in cesarean delivery rates, and the group receiving epidural had significantly better pain relief during labor.
- The use of either epidural, spinal, or combined techniques of regional anesthesia is considered by most obstetric anesthesiologists to be the method of choice during cesarean delivery. In women with severe preeclampsia, general anesthesia carries the risk of

aspiration and failed intubation owing to airway edema, and is associated with marked increases in systemic and cerebral pressures during intubation and extubation.

- Women with airway or laryngeal edema may require awake intubation under fiber-optic observation with the availability of immediate tracheostomy. Changes in systemic and cerebral pressures may be attenuated by pretreatment with labetalol or nitroglycerine injections. It is important to recognize that regional anesthesia is contraindicated in the presence of coagulopathy or severe thrombocytopenia (platelet count $<50,000/\text{mm}^3$).

Prevention of Convulsions

- Magnesium sulfate is the drug of choice to prevent convulsions in women with preeclampsia.[188] The results of 4 recent randomized trials revealed that magnesium sulfate is superior to placebo or no treatment for prevention of convulsions in women with severe preeclampsia. The overall results of the four trials demonstrate that magnesium sulfate prophylaxis, compared with placebo (two trials, 10,795 women), nimodipine (one trial, 1,750 women), and with no treatment (one trial 228 women) in severe preeclampsia, is associated with a significantly lower rate of eclampsia (RR 0.39; 95 percent CI 0.28 to 0.55).Results from one of the largest randomized trials to date, that of 10,141 women with preeclampsia in 33 nations (largely in the third world), has been recently reported. Almost all of the enrolled patients had severe disease by United States standards: 50 percent received antihypertensives before randomization, 75 percent received antihypertensives after randomization, and the remainder had severe preeclampsia or imminent eclampsia.
- Among all enrolled women, the rate of eclampsia was significantly lower in those assigned to magnesium sulfate (0.8 percent versus 1.9 percent, RR; 0.42; 95 percent CI, 0.29 to 0.60). However, among the 1,560 women enrolled in the Western world, the rates of eclampsia were 0.5 percent in the magnesium group versus 0.8 percent in the placebo, a difference that was not significant (RR 0.67; 95 percent CI 1.19 to 2.37).
- There are two randomized placebo-controlled trials evaluating the efficacy and safety of magnesium sulfate in women with mild preeclampsia. [194] [195] One of these trials included 135 women and the other included only 222 women. There were no instances of eclampsia in either group in both of these trials. In addition, the findings of both studies revealed that magnesium sulfate does not affect the duration of labor, and it does not affect the rate of cesarean delivery. However, neither of these studies had adequate sample size to address the efficacy of magnesium sulfate to prevent convulsions. Therefore, whether there is a benefit of magnesium sulfate treatment in women with mild preeclampsia remains unclear. Intravenous magnesium sulfate should be administered during labor and postpartum for all women with severe preeclampsia. This author does not routinely use this therapy in women with mild gestational hypertension or preeclampsia in the absence of symptoms. In women having an elective cesarean delivery, magnesium sulfate is given at least 2 hours before the procedure and continued during surgery and for at least 12 hours postpartum

Control of Severe Hypertension

- The objective of treating acute severe hypertension is to prevent potential cerebrovascular and cardiovascular complications such as encephalopathy, hemorrhage, and congestive heart failure.[2] For ethical reasons, there are no randomized trials to determine the level of hypertension to treat in order to prevent these complications. Antihypertensive therapy is recommended by some for sustained systolic BP values of 180 mm Hg or more, and for sustained diastolic values of 110 mm Hg or more. Some experts recommend treating systolic levels of 160 mm Hg or more, whereas others recommend treating diastolic levels of 105 mm Hg, and still others use a mean arterial BP of 130 mm Hg or more. The definition of sustained hypertension is not clear, and ranges from 30 minutes to 2 hours.
- The most commonly used and advocated agent for the treatment of severe hypertension in pregnancy is intravenous hydralazine given as bolus injections of 5 to 10 mg every 15 to 20 minutes for a maximum dose of 20 mg. Recently, several drugs have been compared with hydralazine in small, randomized trials. Magee and colleagues performed a meta-analysis of 21 trials (893 women); eight trials compared hydralazine with Nifedipine, and five compared hydralazine to labetalol. The results of these trials were the subject of a recent systemic review that suggested that intravenous labetalol or oral Nifedipine are as effective and have fewer side effects than intravenous hydralazine.
- The recommended dose of labetalol is 20 to 40 mg intravenously every 10 to 15 minutes for a maximum of 220 mg, and the dose of nifedipine is 10 to 20 mg orally every 30 minutes for a maximum dose of 50 mg. Sustained BP values of 170 mm Hg systolic or more, or 110 mm Hg diastolic or more require therapy intrapartum. For women with thrombocytopenia and those in the postpartum period systolic values of 160 mm Hg or more, or diastolic readings of 105 mm Hg or more are the recommended thresholds for therapy.[2] For this author, the first-line agent is intravenous labetalol, and if maximum doses are ineffective, oral nifedipine is added.

Mode of Delivery

- There are no randomized trials comparing the optimal method of delivery in women with gestational hypertension-preeclampsia. A plan for vaginal delivery should be attempted in all women with mild disease without other indications for cesarean delivery, and in the majority of women with severe disease, particularly those beyond 30 weeks' gestation.
- The decision to perform cesarean delivery should be based on gestational age, fetal condition, presence of labor, and cervical Bishop score. In general, the presence of severe preeclampsia is not per se an indication for cesarean delivery.

Postpartum Management

- During the immediate postpartum period, women with preeclampsia should receive close monitoring of BP, of symptoms consistent with severe disease, and accurate measurements of fluid intake and urinary output.
- These women usually receive large amounts of intravenous fluids during labor as a result of prehydration before the administration of epidural analgesia, and intravenous fluids given during the administration of oxytocin and magnesium sulfate in labor and postpartum. In addition, during the postpartum period, there is mobilization of extracellular fluid leading to increased intravascular volume. As a result, women with severe preeclampsia, particularly those with abnormal renal function, those with capillary leak, and those with early onset disease are at increased risk for pulmonary edema and exacerbation of severe hypertension postpartum. These women should receive careful evaluation of the amount of intravenous fluids, oral intake, blood products, and urine output, as well as monitoring by pulse oximetry and chest auscultation.
- In general, most women with gestational hypertension become normotensive during the first week postpartum. In contrast, in women with preeclampsia, hypertension often takes longer to resolve. In addition, in some of the women with preeclampsia, there is an initial decrease in BP immediately postpartum, followed by development of hypertension again between days 3 and 6. Antihypertensive drug treatment should be undertaken if the systolic BP is at least 155 mm Hg or if the diastolic is at least 105 mm Hg, with oral nifedipine 10 mg every 6 hours or long-acting Nifedipine. If the BP is well controlled and maternal symptoms are absent, the woman is then discharged home with instructions for daily BP measurements by a home visiting nurse for the first week postpartum or longer as necessary. Antihypertensive medications are discontinued if the BP remains below the hypertensive levels for at least 48 hours. Recently, some authors have suggested that 5 days of oral furosemide therapy (20 mg/dl) enhances recovery and reduces the need for antihypertensive therapy in women with severe preeclampsia
- Severe hypertension or severe preeclampsia may develop for the first time in the postpartum period. Hence, all postpartum women should be educated about the signs and symptoms of severe hypertension or preeclampsia. These women are at increased risk for eclampsia, pulmonary edema, stroke, and thromboembolism. Therefore, medical providers as well as personnel who respond to patient phone calls should be educated and instructed about important information to report to physicians. In addition, women who have persistent severe headaches, visual changes, and epigastric pain with nausea or vomiting, and those with severe hypertension require immediate evaluation and potential hospitalization. These women often require magnesium sulfate for at least 24 hours and antihypertensive therapy. If neurologic symptoms exist, brain imaging is undertaken to rule out the presence of cerebral pathology.

Maternal and Perinatal Outcome with Preeclampsia

- Maternal and perinatal morbidities are substantially increased in women with severe gestational hypertension. Indeed, these women have higher morbidities than women with mild preeclampsia. In addition, the rates of abruptio placentae, preterm delivery (at less than 37 and 35 weeks), and rates of SGA infants in these women are similar to those seen in women with severe preeclampsia. However, whether or not this increase in rate of preterm delivery is a result of early delivery chosen by the physician or because of the disease process itself remains unknown. Therefore, these women should be managed as if they had severe preeclampsia.
- Maternal and perinatal outcomes in preeclampsia are usually dependent on one or more of the following: gestational age at onset of preeclampsia as well as at time of delivery, the severity of the disease process, the presence of multifetal gestation, and the presence of preexisting medical conditions such as pregestational diabetes, renal disease or thrombophilias. In women with mild preeclampsia, the perinatal death rate, rates of preterm delivery, SGA infants, and abruptio placentae are similar to those of normotensive pregnancies. The rate of eclampsia is less than 1 percent, but the rate of cesarean delivery is higher because of increased use of induction of labor.
- In contrast, perinatal mortality and morbidities as well as the rates of abruptio placentae are substantially greater in women with severe preeclampsia.
- The rate of neonatal complications is markedly increased in those who develop severe preeclampsia in the second trimester, whereas it is minimal in those with severe preeclampsia beyond 35 weeks' gestation.
- Severe preeclampsia is also associated with an increased risk of maternal mortality (0.2 percent) and increased rates of maternal morbidity (5 percent) such as convulsions, pulmonary edema, acute renal or liver failure, liver hemorrhage, DIC, and stroke. These complications are usually seen in women who develop preeclampsia before 32 weeks' gestation and in those with preexisting medical conditions.

Counseling Women Who Have Had Preeclampsia in Prior Pregnancies

- We have examined the pregnancy outcomes and incidences of preeclampsia in subsequent pregnancies, as well as the frequency of chronic hypertension and diabetes mellitus in women who had severe preeclampsia (287 women) or eclampsia (119 women) in their first pregnancies (aged 11 to 25 years) compared with 409 women (aged 12 to 25 years) who remained normotensive during their first pregnancies. Each woman had at least one subsequent pregnancy (range, 1 to 11) and was followed for a minimum of 2 years (range, 2 to 24). There was no significant difference in the incidences of diabetes mellitus in the two groups (1.3 versus 1.5 percent). The incidence of chronic hypertension was significantly higher in the preeclampsia patients (14.8 versus 5.6 percent; $p < 0.001$). This difference became even greater for those women followed for more than 10 years (51 versus 14 percent; $p < 0.001$). The incidence of severe preeclampsia was also significantly higher in the second pregnancies (25.9 to 4.6 percent) as well as in the subsequent pregnancies (12.2 to 5.0 percent) of women with preeclampsia.

- In a later report, subsequent pregnancy outcome and long-term prognosis were studied in 108 women who had severe preeclampsia in the second trimester.[206] These women were followed for a minimum of 2 years (range, 2 to 12 years) and had a total of 169 subsequent pregnancies. Fifty-nine (35 percent) subsequent pregnancies were normotensive, and 110 (65 percent) were complicated by preeclampsia. Overall, 21 percent of all subsequent pregnancies were complicated by severe preeclampsia in the second trimester. In addition, these women had a high rate of chronic hypertension on follow-up, with the highest incidence being in those who had recurrent severe preeclampsia in the second trimester (55 percent).
- Hnat et al. reported subsequent pregnancy outcome in women with previous preeclampsia enrolled in a multicenter trial. The rate of recurrent preeclampsia was 17 percent. The authors also noted that these women had a high rate of severe preeclampsia and poor perinatal outcome. In addition, even in those who remained normotensive in their subsequent pregnancy, there was a greater likelihood of adverse pregnancy outcome (preterm delivery, SGA infants, and perinatal death).
- Some women with preeclampsia remote from term may have abruptio placentae. The risk of this complication is increased significantly in those with severe preeclampsia before 34 weeks' gestation and particularly in those who have severe preeclampsia in the second trimester. For patients with preeclampsia complicated by abruptio placentae, the risk of subsequent abruptio ranges from 5 to 20 percent. In addition, these women are at increased risk for subsequent chronic hypertension
- Pregnancy outcome and long-term prognosis were studied in 37 women with severe preeclampsia complicated by pulmonary edema, and 18 of these women had subsequent pregnancies. Ten of the 18 were normotensive, four were complicated by chronic hypertension, and four by preeclampsia; one of the latter women also had pulmonary edema.
- Pregnancy outcome and remote prognosis were also studied in 18 women with severe preeclampsia complicated by acute renal failure. All 18 had acute tubular necrosis, nine required dialysis, and two died within 8 weeks after birth. All patients had serial evaluation of renal function, urine microscopic testing, and electrolyte studies at the onset of acute renal failure and during follow-up. All 16 surviving patients had normal renal function on long-term follow-up (average, 4 years). Four of the 16 women had seven subsequent pregnancies: one ended in miscarriage, one was complicated by preeclampsia at 35 weeks, and five were term pregnancies without complications.
- Pregnancies complicated by HELLP syndrome may be associated with life-threatening complications for both the mother and her infant. Therefore, clinicians should be able to answer questions regarding subsequent pregnancy outcome and long-term prognosis. Women with a history of HELLP syndrome are at increased risk of all forms of preeclampsia in subsequent pregnancies. In general, the rate of preeclampsia in subsequent pregnancies is approximately 20 percent, with significantly higher rates if the onset of HELLP syndrome was in the second trimester. The rate of recurrent HELLP syndrome ranges from 2 to 19 percent, with the most reliable data suggesting a recurrence risk of less than 5 percent. Because of the above-mentioned risks, these women are informed that they are at increased risk for adverse pregnancy outcome (preterm delivery, fetal growth restriction, abruptio placentae and fetal death) in subsequent pregnancies. Therefore, they require close monitoring during subsequent gestations. At present, there is no preventive therapy for

recurrent HELLP syndrome. There are case series describing subsequent pregnancy outcome in women with previous ruptured liver hematomas. We have followed three women with previous ruptured liver hematomas through

four subsequent pregnancies without complications. Other authors reviewed the literature and reported on several such women who had subsequent uneventful pregnancies under close maternal and fetal observation

- Liver function tests were studied in 54 women at a median of 31 months (range, 3 to 101 months) after pregnancies complicated by the HELLP syndrome. Serum levels of AST, LDH, and conjugated bilirubin were found to be normal. However, total bilirubin levels were elevated in 11 (20 percent) of the studied women. The authors of this report suggested the possibility that a dysfunction of the bilirubin-conjugating mechanism represents a risk factor for the development of this syndrome.
- There are 2 reports describing long-term renal function after HELLP syndrome. One of the reports included 23 patients whose pregnancies were complicated by HELLP syndrome and acute renal failure: eight of these women had 11 subsequent pregnancies, with nine resulting in term gestation. All 23 women also had normal BPs and renal function at an average follow-up of 4.6 years (range, 0.5 to 11 years). The other study compared renal function after at least 5 years following HELLP syndrome in 10 patients to the respective findings in 22 patients with previous normotensive gestation. There were no differences in renal function tests between the two groups. These findings suggest that the development of HELLP syndrome with or without renal failure does not affect long-term renal function.

Remote Prognosis

- Patients with preeclampsia should also be counseled regarding future cardiovascular risks and risks for underlying renal disease. There is evidence that women with preeclampsia remote from term are at increased risk for chronic hypertension later in life. In addition, these patients, particularly those with recurrent preeclampsia, are more likely to have underlying renal disease. In a recent report, 86 Japanese women who had severe hypertension, severe proteinuria, or both during pregnancy had a postpartum renal biopsy. The authors found that women who had gestational proteinuria or preeclampsia before 30 weeks' gestation were more likely to have had underlying renal disease.
- Several recent studies suggested that women who develop preeclampsia may be at increased risk for coronary artery disease later in life. Indeed, many of the risk factors and pathophysiologic abnormalities of preeclampsia are similar to those of coronary artery disease. Ramsey et al. demonstrated for the first time, using laser Doppler imaging in vivo, and impaired microvascular function in women 15 to 25 years of age following a pregnancy complicated by preeclampsia. Thus, microvascular dysfunction, which is associated with insulin resistance, may be a predisposing vascular mechanism for both coronary heart disease and preeclampsia. Therefore, pregnancies complicated by preeclampsia may identify women at risk of vascular disease in later life and may provide the opportunity for life style and risk factor modification to alter maternal vascular disease risk