Preeclampsia
Recent Insights
James M. Roberts, Hilary S. Gammill

Abstract—Preeclampsia is a pregnancy complication with serious consequences for mother and infant. The disorder is diagnosed by gestational hypertension and proteinuria but is far more than pregnancy induced hypertension. Preeclampsia is proposed to occur in 2 stages. Stage 1 reduced placental perfusion is postulated as the root cause and to lead to the maternal syndrome, Stage 2. Why perfusion is reduced, how this translates to a maternal disease in some but not all women and what is the linkage of the 2 stages are topics of intense study. In the last decade such studies have provided valuable insights into pathophysiology that now guide ongoing clinical trials. (Hypertension. 2005; 46:1243-1249.)

Key Words: preeclampsia ■ hypertension, pregnancy ■ oxidative stress ■ endothelium

Preeclampsia is a pregnancy complication recognized by new-onset gestational hypertension and proteinuria (see definitions below). The disorder affects both mothers and their infants. Once the disease is evident clinically, it can be cured only by delivery. In developed countries, surveillance for preeclampsia through prenatal care allows for early identification and intervention via delivery. This management has changed little in the last 100 years, and it is very effective at reducing maternal mortality. However, maternal morbidity remains great with preeclampsia, which continues to be one of the leading causes for the admission of pregnant women to intensive care units in the developed world. Furthermore, fetal mortality and morbidity is considerable, related to the effects of the disease on the fetus as well as prematurity. The indicated delivery of women to prevent the progression of preeclampsia is responsible for 15% of all preterm births. In developing countries, where inadequate prenatal care limits preeclampsia surveillance, maternal mortality is common, accounting for 50 000 deaths yearly.

The hypertensive disorders of pregnancy include hypertension that antedates pregnancy, chronic hypertension, and gestational hypertension occurring uniquely during pregnancy. When the gestational hypertension is accompanied by new-onset proteinuria, the disorder is termed preeclampsia, and when not associated with proteinuria, transient hypertension of pregnancy. If the woman with chronic hypertension also manifests evidence of preeclampsia, this is classified chronic hypertension with superimposed preeclampsia. Eclampsia is the occurrence of seizures in women with preeclampsia.

These criteria have been extraordinarily useful to aid in recognizing pregnant women at risk. Greatest risk for mother and baby is present with preeclampsia, and the risk for chronic hypertensive pregnancy is primarily with superimposed preeclampsia. However, the attention to hypertension has, for many years, limited research attention to primarily mechanisms of hypertension. This has not been helpful. In the last 2 decades, appreciation that preeclampsia is a multisystemic syndrome characterized by vasoconstriction, metabolic changes, endothelial dysfunction, activation of the coagulation cascade, and increased inflammatory response, to mention only some of the organ systems involved, has redirected research. As a result, progress in understanding the disorder has accelerated greatly, with attendant optimism for potentially effective treatments. In this article, we consider this recent progress and its clinical implications.

Preeclampsia: A Two-Stage Disorder
A 2-stage model of preeclampsia (Figure 1) has been proposed as useful conceptually to address its pathophysiology. Stage 1 of preeclampsia, reduced placental perfusion, is considered the “root cause.” This then somehow translates, in some but not all women, into stage 2: the multisystemic maternal syndrome of preeclampsia. Although much still remains unknown in both of these areas, the major questions are: (1) why does reduced placental perfusion result in preeclampsia in only some women, and (2) what links stages 1 and 2?

Stage 1 of Preeclampsia: Reduced Placental Perfusion
Clinical Evidence
More than 60 years ago, Ernest Page formalized the concept that placental perfusion was reduced in preeclampsia. Evi-
Mechanisms

The failed placental site vascular remodeling of preeclampsia has been the target of intense scrutiny. It appears that the remodeling of these vessels is largely a result of trophoblast invasion, in particular, endovascular invasion. Cellular control of cytotrophoblast invasion depends on interactions between maternal decidua and fetal trophoblast. Local oxygen tension and immune-mediated interactions are primary determinants of the process, and their common mechanism may be through apoptosis.11

Stage 2 of Preeclampsia: More Than Pregnancy-Induced Hypertension

Pathological and Pathophysiological Changes

Pathological changes in women dying with eclampsia present a common theme: they are all consistent with profoundly reduced perfusion.22 In the liver and adrenal, reduced perfusion is indicated by infarction, necrosis, and intraparenchymal hemorrhage. Endocardial necrosis is present in the heart, similar to that present with hypovolemic shock, the prototypic-reduced perfusion disorder. The pathological changes in the kidney are termed glomerular endotheliosis and consist largely of marked swelling of glomerular endo-

Oxygen tension in the intervillous space is low until 10 to 12 weeks after conception, when maternal vessels begin to perfuse the intervillous space.13 With this, the oxygen tension increases dramatically, as does the concentration of reactive oxygen species. Maternal antioxidant capacity determines the ability of the decidual/trophoblast interface to accommodate. It is proposed that if the capacity is not sufficient, impaired invasion, poor placental perfusion, and perhaps preeclampsia can result.13 There are many consequences to this increase in oxygen delivery. Data obtained in vitro suggest that increased oxygen tension triggers a change in trophoblast behavior and phenotypic expression from primarily proliferative to invasive.14 Additionally, at higher oxygen tension, cytotrophoblast cells that line maternal vessels further develop a phenotype similar to vascular endothelial cells, expressing cadherins, integrins, and other cellular adhesion molecules. Expression of these molecules is impaired in trophoblastic cells in preeclampsia,15 which may be because of an inherent inability of these cells to transform, or to a lower antioxidant capacity in preeclampsia. Other cellular factors such as matrix metalloproteinase-916 also influence the success of decidual invasion.

In addition to oxygen tension as a major regulator of trophoblast differentiation and invasion, immune mechanisms play an important role. The immune cells that predominate in the decidua are a specific population of uterine natural killer (uNK) cells. Killer immunoglobulin receptors (KIRs) on these maternal uNK cells interact with specific fetal trophoblast cell markers, influencing trophoblast invasion. Trophoblastic human leukocyte antigen C (HLA-C) (a major histo-compatibility complex class I molecule) is central in the trophoblast/decidual interaction.17,18 Specific genotypic combinations of KIR and HLA-C result in an increased risk of preeclampsia. This combination consists of trophoblast HLA-C molecules that interact with an inhibitory KIR, leading to excessive inhibition of uNK cell activity and therefore decreased invasion of trophoblasts.19 It is increasingly apparent that normal placentaion requires a balance of inhibition and activation of uNK cells that is mediated by maternal and fetal factors.

Placental apoptosis may be the final common pathway for these mechanisms. Placentas of preeclamptic patients show more overall apoptosis than controls.20 Apoptosis also leads to the release of syncytiotrophoblast microfragments into the maternal circulation, which is accelerated in preeclampsia.21

Figure 1. Two-stage model of the pathophysiology of preeclampsia. The model indicates preeclampsia as occurring in 2 stages. The initiating abnormality (stage 1) is failed vascular remodeling of the vessels that supply the placental bed. This is linked to the maternal syndrome of preeclampsia (stage 2).
thelial cells sufficient to occlude the capillary lumen. This is accompanied by minimal changes in the renal podocytes. This change is important because it is present in no other form of hypertension, indicating preeclampsia is not merely an unmasking of prepregnancy hypertension. Additionally, the involvement of primarily endothelium points toward this tissue as an important target in the disorder.

Pathophysiological changes support the reduced perfusion concept. Perfusion is reduced to virtually any organ examined, including the uterus. Reduced uterine blood flow further reduces placental perfusion, resulting in a feed-forward loop consistent with the clinical course of preeclampsia. This is a disease that never gets better, only worse, and when it begins to worsen, it worsens rapidly.

Perfusion decreases secondary to vasospasm, activation of the coagulation cascade with the formation of occlusive microthrombi, and loss of fluid from the intravascular space. Vasospasm is not secondary to unique pressors or to an increase in usual pressors. Rather, women with preeclampsia are uniquely sensitive to any pressor agent. Quite importantly, the increased pressor sensitivity, activation of the coagulation cascade, and loss of vascular integrity are evident in groups of women before the clinical manifestations of the disorder. This has led to the concept that endothelial dysfunction, which could explain all of the changes described, is a central pathophysiological feature of the disorder.

This hypothesis is also supported by altered endothelial-mediated vasodilatation, when vessels from several sites of preeclamptic women are examined ex vivo. Furthermore, a myriad of markers of endothelial injury or dysfunction are present in women with preeclampsia and, in many cases, precede clinically evident disease supporting a causal role. Although most models of endothelial activation or dysfunction in preeclampsia posit that placental products produced in response to reduced perfusion alter endothelial function, it is also likely that deficiency of repair secondary to reduced mobilization of endothelial progenitor cells may also be relevant. Endothelial activation is only one component of a generalized activation of inflammatory responses that is characteristic of pregnancy (sometimes showing changes nearly as pronounced as those seen in sepsis) and further accentuated in preeclampsia.

Striking metabolic changes also characterize preeclampsia. These include a dyslipidemia with elevated triglycerides, free fatty acids, and LDL cholesterol, and reduced HDL cholesterol, with an increased prevalence of low dense LDL. Insulin resistance and uric acid, other components of the metabolic syndrome, are also increased in preeclampsia. Many of these changes, including elevated free fatty acids and uric acid, can be demonstrated from very early pregnancy. Whether they antedate pregnancy has not been established. Self-reported history of hypercholesterolemia has been reported in nonpregnant women who later develop preeclampsia.

Uric acid has received increasing attention as potentially relevant not merely as a marker of cardiovascular disease but as causally important. For example, rats in which uric acid is increased experimentally have increased blood pressure.

Whether hyperuricemia, one of the earliest and most consistent findings in preeclampsia, is causally important is being re-evaluated. A recent study by our group found that in women with gestational hypertension, uric acid was an indicator of increased adverse fetal outcome even in the absence of proteinuria.

**Maternal Fetal/Placental Interactions in Preeclampsia**

Not all women with reduced placental perfusion develop preeclampsia. Pregnancies complicated by intrauterine growth restriction, the failure of infants to exercise their full growth potential, also have a similar reduction of placental perfusion. The failed remodeling of the uterine vessels supplying the placenta that is characteristic of preeclampsia is also present in intrauterine growth restriction, as well as in about one third of cases of spontaneous preterm birth without the clinical manifestations of preeclampsia. This has led to the concept that reduced placental perfusion must interact with maternal factors to result in clinical preeclampsia (Figure 2). These factors are proposed to be genetic, behavioral, and environmental. They are modified by the normal physiological changes of pregnancy, of which the increased inflammatory response may be particularly relevant. Conditions recognized to increase the risk of preeclampsia include obesity, hypertension, diabetes, hyperhomocysteinemia, increased androgens, and black race. Of course, these are all risk factors for cardiovascular disease in later life. The similarities between the pathophysiological features of preeclampsia and cardiovascular risk factors suggest a relationship between these conditions that is supported by epidemiological follow-up studies.

The genetic predisposition to preeclampsia has attracted much attention. Preeclampsia is clearly inherited. The frequency of preeclampsia in mothers, daughters, sisters, and granddaughters is 2 to 5× higher than in mothers-in-law,
daughters-in-law, or control populations. Attempts to impede genetic mechanisms are problematic because the syndrome occurs in only half of the population and is not manifest until reproductive years and then only in women who become pregnant. In a summary of inheritance studies, Arrangrimsson concluded that within these limitations, data were consistent with a major dominant gene with variable penetrance or multifactorial inheritance. The major contribution is from the maternal genome; however, fetal (paternal) genes are also contributors. Attempts to identify preeclampsia gene(s) have used hypothesis-driven searches for candidate genes and genome-wide searches. Several function-perturbing polymorphisms of candidate genes are reported as more common in women with a history of preeclampsia. These include genes relevant to thrombophilias, folate metabolism, lipid metabolism, oxidative stress, and components of the renin-angiotensin system. The interesting feature of all of these candidate genes is the inconsistency with which they are found in different populations. As an example, the function-perturbing polymorphism of the methylenetetrahydrofolate reductase gene C677T has been examined in >27 studies, with widely diverging results in different populations. This may represent population differences consistent with the heterogeneity of preeclampsia but also reflects differing definitions of preeclampsia and, interestingly, year of publication. Early reports support a relationship, whereas more recent reports do not, suggesting publication bias. This same inconsistency characterizes reports of all genetic polymorphisms associated with preeclampsia.

Genome-wide searches are in progress. Reports of significant linkages between preeclampsia and loci on several chromosomes have been reported in studies from Iceland, Australia, the Netherlands, and Finland. As with candidate genes, the results are inconsistent. Linkage to chromosome 2 was found in 3 studies. In 2 of these, it could not be excluded that the sites were the same, but in the third, the site was clearly different. In the Finnish study, linkage to chromosome 9 was to a site similar to that associated with type 2 diabetes in studies from China and Finland. A recent study indicates expression of highly polymorphic genes relevant to implantation with missense mutations cosegregating with preeclampsia in a chromosomal site identified as related to preeclampsia in Dutch studies. Interestingly, most of the preeclampsia gene candidates are not localized to these sites. These studies support the heterogeneity of preeclampsia and its multifactorial inheritance.

The concept that maternal factors interact with reduced placental perfusion to produce the preeclampsia syndrome provides 2 especially important insights. First, it can help explain the diverse fetal manifestations of preeclampsia. Preeclampsia is associated with growth-restricted infants; however, this occurs in only one third of cases. In preeclamptic pregnancies terminating after 37 weeks of gestation, there is actually an excess of large infants. The maternal/fetal/placental interaction model proposes that the contribution of maternal and fetal/placental factors may vary in proportion. Thus, in the woman with abundant predisposing factors, even minor reduction in placental perfusion is sufficient for stage 2, whereas profound reductions in placental perfusion will result in the preeclampsia syndrome even in a woman with minimal predisposing factors. Second, the identification of these maternal factors provides specific targets for prevention of preeclampsia that are relevant to a subset of at-risk women.

The Linkage of Stages 1 and 2
A key question in the 2-stage model of preeclampsia is what is the linkage of the 2 stages? This is the “holy grail” of preeclampsia research because identifying such linkage would provide a target for therapy common to all cases of preeclampsia regardless of predisposing factors. Over the years, numerous candidates have been considered and discarded. The search for unique factors present in the circulation of women with preeclampsia, “Substance X,” occupied at least a generation of investigators. The idea was eventually abandoned after numerous false starts in favor of an excess of usual factors such as cytokines, growth factors, or placental hormones. The concept of unique placental products, nonetheless, remains viable with the hypothesis that microvillus particles, likely the product of syncitiotrophoblast apoptosis, are present in excess in the blood of women with preeclampsia. It is proposed that these products interact with and activate circulating inflammatory cells or perhaps directly affect endothelial function. Several cytokines and other inflammatory markers that could alter endothelial function are increased in the blood of women with preeclampsia. However, neither increased placental mRNA nor uterine vein concentrations of relevant cytokines support a placental origin for these molecules. There is evidence for increased activation of inflammatory cells, which could take place during passage through the intervillous space. These cells could then be the source of increased inflammatory molecules. Placental hormones including estrogen, progesterone, and human placental lactogen have been suggested as the linkage, but in general, their role has been inconsistently supported. The role of aberrations of the renin-angiotensin system has been considered for many years. Several reports have identified autoantibodies to the angiotensin subtype 1 receptor (AT1) angiotensin antibodies in women with preeclampsia. These antibodies can activate the AT1 receptor in vitro with resultant increases in tissue factor and NADP-H oxidase activity. The origin of these autoantibodies and the natural history of their appearance and disappearance are not as yet determined. A preeclampsia-like syndrome can be induced in rats genetically modified to increase angiotensin production. Interestingly, these rats evidence an increase in autoantibodies to the AT1 receptor.

Recent findings of increased concentrations of the soluble receptor for the angiogenic factors vascular endothelial growth factor and placental growth factor (s-Flt) in preeclampsia suggest that this molecule, which can be produced by the placenta in response to hypoxia, may be involved in the linkage. When the growth factors are bound to s-Flt, they are inactive. Animal experiments indicate that administration of s-Flt to pregnant rats results in hypertension and proteinuria. The conclusion that s-Flt is solely responsible for the linkage must be tempered by the finding that s-Flt is
not increased in all women with preeclampsia, including some with even severe disease.72

Oxidative stress, the excess of reactive oxygen species beyond the buffering capacity of endogenous antioxidants, is considered a prime candidate for linkage of the 2 stages. Most of the suggested linkages could contribute to or be stimulated by oxidative stress. Cytokines cause the release of free radicals73 as part of their mechanism of action, whereas activated monocytes and neutrophils release free radicals when in contact with activated endothelium. NADPH activation by angiotensin autoantibodies would result in the generation of free radicals. Oxidative stress triggers placental apoptosis,74 causing the release of microvesicular particles containing oxidized lipids, which can then act systemically. The growth factor inhibitor s-Fli is increased with hypoxia,75 which, when accompanied by reperfusion, can also increase the generation of free radicals.

Oxidative stress is proposed as relevant to many diseases, and a role in preeclampsia has been entertained for ~50 years.76,77 Abundant evidence supports the presence of oxidative stress in preeclampsia.31 However, there is controversy regarding lipid markers of oxidative stress that are increased in the disorder.78 Lipid peroxides and other oxidatively modified lipids such as isoprostanes have been reported to be increased in blood and tissues of women with preeclampsia for many years.31 However, oxidative modifications of these lipids can occur independent of oxidative stress either ex vivo or by enzymatic modification of lipids.78 This has raised the question as to the relevance of increases of these materials to oxidative stress in preeclampsia. Nonetheless, there is abundant other evidence for oxidative stress in preeclampsia, including protein products of oxidative stress in maternal79 and fetal tissues80 as well as antibodies to oxidatively modified LDL.81 Furthermore, concentrations of the lynchpin antioxidant ascorbate are reduced in women with preeclampsia and women destined to develop preeclampsia.82

The ultimate test of the role of oxidative stress is whether reduction or prevention of oxidative stress can ameliorate or prevent endothelial dysfunction and the maternal preeclampsia syndrome. As with all other interventions, the use of antioxidants after clinical evidence of preeclampsia was unsuccessful.83 However, in a small trial of antioxidant therapy, 1000 mg of vitamin C and 400 IU of vitamin E administered from 20 weeks gestation not only reduced evidence of endothelial activation but also significantly reduced the incidence of preeclampsia.84 Although promising, only 79 women actually received therapy in this study. Also, another small study did not demonstrate benefit with 50 treated and control subjects.85 Larger international multicenter studies testing the efficacy of therapy and definitively establishing proof of safety in pregnancy are now in progress.

Clinical Implications
The fact that stage 1 of preeclampsia, including abnormal placental bed vascular remodeling, is present in settings other than preeclampsia indicates that understanding this phenomenon has importance beyond preeclampsia. It also suggests that a useful target for investigation would be the understand-
References


Preeclampsia: Recent Insights
James M. Roberts and Hilary S. Gammill

Hypertension. 2005;46:1243-1249; originally published online October 17, 2005;
doi: 10.1161/01.HYP.0000188408.49896.c5

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/46/6/1243

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/