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Preeclampsia—A Pressing Problem: An Executive Summary of a National Institute of Child Health and Human Development Workshop

John V. Ilekis, PhD, Uma M. Reddy, MD, MPH, and James M. Roberts, MD

On September 21 and 22, 2006, the National Institute of Child Health and Human Development of the National Institutes of Health sponsored a 2-day workshop titled "Preeclampsia—A Pressing Problem." The purpose of the workshop was to bring together leaders in the field to present and discuss their diverse research areas, which ranged from basic science to clinical trials and management, and to identify scientific gaps. This article is a summary of the proceedings of that workshop. Although much progress is being made in understanding the underpinnings of preeclampsia, a number of research gaps are identified that, if filled, would hasten progress in the field. It is the overall consensus that preeclampsia is a multifactorial disease whose pathogenesis is not solely vascular, genetic, immunologic, or environmental but a complex combination of factors. In addition, a number of specific scientific gaps are identified including insufficient multidisciplinary and collaborative research, clinical trials and studies of patient management, and a lack of in-depth mechanistic research. The research community needs to focus on these gaps to better understand the disease, with the ultimate goal of preventing the disorder.

KEY WORDS: Preeclampsia, workshop, research, trials, gaps.

Preeclampsia is a pregnancy-specific, multisystemic disorder that occurs in about 4% of all live-birth pregnancies in the United States, and it is a leading cause of maternal and fetal mortality and morbidity.^{1,2} Moreover, preeclampsia is the primary reason for indicated preterm deliveries before 37 weeks of gestation.² Although advances have been made in the clinical management of preeclampsia to prolong the delivery time for improving neonatal outcome, delivery is still the only definitive treatment.³ Unfortunately, premature delivery of the fetus can be associated with adverse sequelae for

the infant. Consequently, balancing maternal and fetal risks in the management of early-onset preeclampsia is a challenge for care providers.

Pathological examination of the placental bed has shown that most women with preeclampsia have shallow invasion and poor remodeling of the uterine vasculature, resulting in reduced placental perfusion. This finding suggests that this defect is important in the development of the disease.^{4,5} The current and widely accepted concept is that the placenta, in response to hypoxia/ischemia caused by poor placental perfusion, releases factors into the circulation that damage the endothelium sufficiently to cause the maternal syndrome.⁶ However, this defect is also common in other pregnancy disorders such as fetal growth restriction and preterm birth; hence, alone, it is not sufficient to cause preeclampsia and undoubtedly requires other contributing factors.⁵⁻⁹ In this regard, it is postulated that predisposing maternal factors, whether they are genetic, behavioral, or environmental, act together in combination with poor placental perfusion to produce the disease.⁶ Nonetheless, the mechanism(s) by which abnormal remodeling of the uterine vasculature occurs is an ongoing and intense area of research because

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of the high incidence in preeclampsia and other common pregnancy disorders.

One way reduced placental blood flow is postulated to be linked to preeclampsia is through oxidative stress generated as a result of placental hypoxia and reperfusion.⁹ Accumulating evidence over many years indicates increased oxidative stress in the disease, and this notion has stimulated clinical trials of antioxidant therapy with vitamins C and E.¹⁰ Although 1 small trial has shown benefit, more recent larger trials have shown no benefit.¹¹⁻¹³ However, the largest clinical trial, the Combined Antioxidant and Preeclampsia Prediction Study described later in the article, is still ongoing. In addition, other areas in the study of the pathogenesis of preeclampsia appear promising and include some of the following. The immune system appears to play an important role. For example, epidemiological evidence has suggested that exposure to paternal antigen is protective.¹⁴ Interestingly, activating autoantibodies to the angiotensin-2 type 1 receptor has been identified in many preeclamptic women and is associated with abnormal remodeling of the uteroplacental vasculature.^{15,16} A heightened inflammatory response is believed to occur in preeclampsia perhaps due to excessive shedding of syncytiotrophoblast microparticles into the maternal circulation because of enhanced placental apoptosis.¹⁷ Aberrant placental natural killer and trophoblast cell interactions are thought to play an important role in the poor remodeling of the uteroplacental vasculature.¹⁸ In addition, a very active area of current research is angiogenic factors and, in particular, their endogenous antagonists.^{19,20} Increased concentrations of angiogenic antagonists and a reduced concentration of angiogenic agonists are present before clinical disease, concentrations correlate with severity of the disease, and administration of these antiangiogenic factors can induce the disease in an animal model. Furthermore, preeclampsia likely has a genetic component since its incidence is increased among family members, and a number of susceptibility loci have been reported.²¹ Although these findings from different areas of research support the contention that preeclampsia appears to be a multifactorial disease, it is unclear whether these proposed different etiologies are truly disparate from one another or if they share some degree of relationship and, if so, to what extent.

On September 21 and 22, 2006, the National Institute of Child Health and Human Development of the National Institutes of Health sponsored a 2-day workshop titled "Preeclampsia—A Pressing Problem." The workshop brought together leaders in the field to present and discuss their diverse research areas and to

identify significant scientific gaps while stimulating dialogue and future collaborations. This article summarizes the proceedings of that workshop. The first section is a summary of the research topics. The second section presents research gaps based on group discussions as well as individual opinions.

RESEARCH TOPICS

Overview

Patient advocacy group. The Preeclampsia Foundation is a nonprofit organization representing more than 200 000 American women per year who develop preeclampsia (a number equal to those affected by breast cancer; about 1 in 12 pregnancies). It is the primary US patient advocacy group for preeclampsia and other hypertensive disorders of pregnancy. The goal of the foundation is to improve diagnoses in women with preeclampsia and related complications and to ensure optimum care based on knowledge available. Their current focus is to support research to develop broadly accepted, evidence-based guidelines and to improve health services through greater quality-of-care programs and provider and patient education.

Epidemiologic aspects of preeclampsia. Epidemiological research underscores the complex and multifactorial nature of preeclampsia. The best established protective factor is a prior birth, suggesting that maternal immune tolerance to paternal antigens may play an etiologic role. The protective effect of a previous birth is lost when a subsequent pregnancy is conceived with a new partner or after a long interpregnancy interval.^{14,22,23} The protective role of exposure to paternal antigens is supported by a study of nulliparous women, in which a prior termination of pregnancy with the same father as the index pregnancy was half as likely to be associated with preeclampsia as pregnancies of women who had a prior termination of pregnancy with a different partner. Interestingly, the subjects' preeclampsia risk associated with a different partner was equivalent to that of primigravidas.²⁴ Furthermore, reduced exposure to paternal antigen by limited exposure to paternal sperm is also a risk for the development of preeclampsia. Women who conceive after a brief period of sexual cohabitation, by nonpartner donor insemination, by oocyte embryo donation, or by intracytoplasmic sperm injection, all manifest an increased risk of preeclampsia.²²

Epidemiological data also support the pathophysiological evidence characterizing preeclampsia as a condition of excessive systemic inflammation. Conditions such as asthma and obesity, which are both associated with inflammation, increase the risk of preeclampsia. Recent work suggests that women with moderate to severe asthma symptoms, regardless of asthma diagnosis or treatment, are at increased risk of preeclampsia compared with women with no symptoms.²⁵ Similarly, it is increasingly evident that obesity, a well-established risk factor for preeclampsia, is associated with chronic and low-grade inflammation. Several other preeclampsia risk factors are known to be associated with inflammatory response and to further support this relationship. Thus, preeclampsia is more common with maternal infections (eg, malaria, cytomegalovirus, chlamydia), insulin resistance, and an adverse lipid metabolic profile.²²

Observational studies have examined the relationship of regular leisure time exercise on the risk of preeclampsia. All show a consistent risk reduction of at least 50% for women who reported exercise during pregnancy versus those who did not, although the mechanism underlying these findings is speculative.^{26,27} If supported by intervention trials, exercise may be a simple interventional approach for decreasing the risk of preeclampsia.

Definition and diagnosis of preeclampsia. The selection of hypertension and proteinuria as diagnostic indicators of preeclampsia is historical because these signs were first recognized to precede eclampsia.²⁸ Although these indicators define pregnancies at increased risk, they alone may not be sufficiently specific to identify adequately the disease for research purposes. It would be useful to identify other criteria that might increase specificity. In this regard, it has recently been reported that elevated uric acid in women with gestational hypertension and proteinuria defined a higher risk of adverse fetal outcomes.²⁹ Gestational hypertension with hyperuricemia, but without proteinuria, identified these adverse outcomes as well as hypertension and proteinuria without hyperuricemia. These findings emphasize the value of evaluating additional clinical or laboratory findings as diagnostic criteria to increase specificity to facilitate research studies.

It is quite likely that there are subsets of preeclampsia. Identifying these subsets should facilitate understanding the disorder, as it did for better understanding diabetes. Unfortunately, investigators continue to combine 2 of the most different forms of preeclampsia, that is, preeclampsia occurring in the first and later pregnancies.

Epidemiologically, these groups are very different. Later in life, cardiovascular disease occurs earlier and more commonly in women with preeclampsia as multipara.³⁰⁻³² Renal biopsy studies indicate a higher percentage of underlying renal disease in women with preeclampsia as multiparas than as primiparas.³³ Studying only primiparas or separating outcomes of primiparous or multiparous women can increase specificity. Furthermore, is early-onset preeclampsia the same disorder as late-onset preeclampsia? Is severe preeclampsia the same as mild preeclampsia? Is preeclampsia with intrauterine growth restriction (IUGR) the same as preeclampsia without IUGR? For early-onset preeclampsia, the data are fairly compelling. Epidemiologically, preeclampsia after 37 weeks' gestation is associated with larger not smaller babies.³⁴ The recurrence rate for early-onset preeclampsia is much higher than for late-onset preeclampsia; early onset before 37 weeks' gestation also predicts an increased risk of preterm birth and IUGR in subsequent pregnancies.^{35,36} Furthermore, early-onset preeclampsia also presents a greater risk of cardiovascular disease in later life.³⁰ These increased risks are not present with term preeclampsia. Investigators should begin to explore subsets of preeclampsia, looking for differences in their pathophysiology.

Placental Biology

Vascular remodeling of the maternal-fetal interface. The human placenta contains a specialized population of epithelial progenitors (ie, cytotrophoblasts [CTBs]) that, upon differentiation, acquire tumor-like properties that enable uterine invasion, penetration, and remodeling of the spiral arteries, with subsequent rerouting of maternal blood flow to the placenta.³⁷⁻³⁹ During the remodeling of the vessels, CTBs acquire vascular-like qualities and replace the endothelial cells of the vessels. In addition, several vascular endothelium growth factor (VEGF) family members work cooperatively to promote CTB survival and invasion.⁴⁰ Preeclampsia is associated with defects in CTB acquisition of a vascular-like phenotype and production of VEGF family members.^{38,41} Recent work also suggests that the expression of semaphorin-3 family members, another class of molecules with vasculogenic and angiogenic functions, is dysregulated in preeclampsia (Fisher, unpublished data). Hence, perturbations in vasculogenic and angiogenic signaling pathways suggest a mechanism by which placentation goes awry in this syndrome.

Villous morphometry. Quantitative stereological morphometric techniques can be used to assess the potential functionality of a tissue or entire organ. Previous stereological quantification of vascular and villous features in preeclampsia and IUGR placentas suggested either morphological similarities or differences in villous and capillary surface areas between control and preeclampsia cases.^{42,43} The latest results suggest that IUGR may be responsible for numerous villous and vascular deficiencies, but isolated preeclampsia is associated only with disrupted terminal villi volume. In addition, there are no interactive effects when both preeclampsia and IUGR coexist; changes observed in preeclampsia with IUGR appear to be due to IUGR and not preeclampsia.⁴⁴ By using 34 weeks (the period of greatest morphological change) as a separator between early- and late-onset preeclampsia, it is possible to explore when the observed changes in isolated preeclampsia cases might have occurred. Late-onset preeclampsia demonstrates no influence on placental morphology compared with gestational age-matched controls, although changes in villous membrane thickness were present. In marked contrast, early-onset preeclampsia is associated with a significant reduction in placental weight, total placental volume, and numerous villous and vascular features.⁴⁵

The morphological similarity of placentas from late-onset preeclampsia and placentas from gestational age-matched controls supports the existence of 2 subsets of preeclampsia and the hypothesis that late-onset preeclampsia is a maternal disorder rather than a placental disease resulting from disrupted angiogenesis. Both early-onset preeclampsia and IUGR are associated with significant placental morphological disruption contributing to altered fetal growth.

Mediators of Preeclampsia: The Immune System

Inflammatory responses. The inflammatory response is a coordinated response to danger signals, which involves not only inflammatory leukocytes but also other cells and systems such as endothelial cells. In addition, the coagulation and complement systems as well as various metabolic responses (especially those associated with arterial disease in nonpregnancy) may be activated.⁴⁶ Systemic inflammation is part of normal pregnancy, is detected early in the first trimester, and changes as pregnancy progresses.^{47,48} The response is significantly enhanced in preeclampsia relative to normal pregnancy.⁴⁷ It includes

activation of the endothelial system, which is an arm of the inflammatory system. The pregnancy-derived stimuli to systemic inflammation are probably multiple and not necessarily the same at different gestational ages.

Microparticles derived from syncytiotrophoblast cells may play an important role in stimulating the systemic inflammatory response. Shedding of syncytiotrophoblast fragments, microparticles, and cell-free DNA and RNA into the maternal circulation throughout pregnancy is believed to result from normal renewal and repair, mediated by apoptosis. In preeclampsia, there is increased syncytial apoptosis owing to the placental hypoxia and the shedding of necrotic debris.¹⁷ Consequently, significantly more syncytiotrophoblast-derived debris circulates in preeclampsia compared with normal pregnancy.¹⁷ It is presumed that monocytes and dendritic cells in the maternal circulation clear the debris, becoming activated and proinflammatory. Preparations of syncytiotrophoblast microparticles stimulate the production of inflammatory cytokines (tumor necrosis factor, interleukin-12, interleukin-18, and interferon) by peripheral blood mononuclear cells from nonpregnant individuals.⁴⁹ In vitro preparations of trophoblast microparticles have been demonstrated to be highly disruptive to cultured endothelial cells, leading to an antiangiogenic state that in vivo would further contribute to the clinical features of preeclampsia.⁵⁰ Nonetheless, there are many unanswered questions regarding the role of microparticles: How do microparticles stimulate inflammatory responses? Where and how are they cleared? Can they be processed and presented to immune cells, perhaps in nonclassical ways? More research in this promising area is warranted.

Natural killer cells and human leukocyte antigens. It is compelling to think that uterine natural killer (NK) cells rather than T cells provide the principal means by which the maternal immune system could regulate trophoblast function since trophoblast cells lack the classical T-cell human leukocyte antigen (HLA) ligands, HLA-A and HLA-B.^{18,51,52} In contrast to the syncytiotrophoblast, which expresses no major histocompatibility complex (MHC) antigens on its surface, extravillous trophoblast (EVT) cells express an unusual combination of HLA class 1 molecules (HLA-C, HLA-G, and HLA-E). In humans, uNK cells express an array of receptors called killer immunoglobulin-like receptors (KIR), some of which are known to bind to the HLA class 1 molecules expressed by EVT cells. These KIR can be either activating or inhibitory, and the function of the NK cell

depends on the overall balance of these signals. HLA-C is the only known polymorphic MHC molecule expressed by EVT cells and is the dominant ligand for KIR expressed by uterine NK cells. KIR haplotypes comprise 2 groups, A and B; these differ principally by having additional activating receptors in the B haplotype. In any pregnancy, the maternal KIR genotype could be AA (no activating KIR) or AB/BB (presence of between 1 and 5 activating KIRs). The HLA-C ligands for KIR on EVT cells may belong to 2 groups, C1 and C2, which are defined by a dimorphism at position 80 of the $\alpha 1$ domain. This maternal-fetal immunological interaction, occurring at the site of placentation, involves 2 polymorphic gene systems, maternal KIR and fetal HLA-C molecules. Uterine NK-cell function is thus likely to vary in each pregnancy.

Some KIR/HLA-C combinations might be more favorable to trophoblast cell invasion, resulting in a greater increase in uteroplacental blood flow than others because of the overall signals that the NK cell receives. This notion is supported by findings in preeclampsia in which there is an association with an increased frequency of maternal KIRs of the AA genotype but only when this is combined with the presence of an HLA-C2 allotype in the fetus.⁵³ These genetic results translate to functional events at the implantation site by a stronger inhibitory signal delivered to NK cells by the HLA-C2 compared with the HLA-C1. Consequently, in pregnancies with a fetus that expresses HLA-C2, the strong inhibitory signal needs to be overcome for sufficient invasion to occur, and this will happen if the mother has activating KIR (AB/BB genotype); otherwise, the fetoplacental blood supply will be inadequate. Thus, it can be argued that screening for particular KIR/HLA-C combinations may be useful for ascertaining the degree of risk for developing preeclampsia.

Angiotensin receptor-activating autoantibodies. Numerous studies have focused on circulating factors secreted by the placenta that contribute to the maternal syndrome associated with preeclampsia. Other studies implicate the maternal immune system, particularly the production of autoantibodies that activate angiotensin receptor 1 (AT1). In 1999, Wallukat et al¹⁵ reported that sera from women with preeclampsia contain autoantibodies that react with AT1 receptors in a stimulatory fashion. Their important findings have been confirmed and extended in numerous studies showing that these autoantibodies activate AT1 receptors on cardiac myocytes, trophoblast cells, endothelial

cells, mesangial cells, vascular smooth cells, and Chinese hamster ovary cells.⁵⁴⁻⁵⁶

It has recently been demonstrated that the introduction of these autoantibodies into pregnant mice results in hypertension, proteinuria, and increased production of fms-like tyrosine kinase 1 (sFlt-1), classic features of preeclampsia (Zhou, unpublished data). Altogether, these studies show that these autoantibodies activate AT1 receptors on a variety of cell types and provoke biological responses that are relevant to the pathophysiology of the disease. Available evidence indicates that the biological properties of these autoantibodies can be blocked by a 7-amino-acid peptide that corresponds to a specific epitope associated with the second extracellular loop of the AT1 receptor. This fact may have immediate therapeutic implications and also suggests a common immunological origin for these autoantibodies in different individuals. If AT1 receptor-activating autoantibodies play a significant role in the etiology and pathophysiology of preeclampsia, it may one day be possible to block this antibody response and thus either forestall or prevent the onset of symptoms.

Mediators of Preeclampsia: Other Factors

Placental ischemia-hypoxia. There is considerable data that uteroplacental oxygen delivery in preeclampsia is likely to be reduced relative to placental and/or fetal oxygen consumption, thereby rendering a relatively hypoxic intervillous space and placenta. This is supported by recent molecular data demonstrating that both hypoxia-inducible transcription factors (HIFs) HIF-1 and -2α , the master regulators of the cellular response to hypoxia, are increased in the placentas of preeclamptic women.⁵⁷ In addition, numerous downstream genes that are known to be regulated by HIFs are increased in the placentas of preeclamptic women, and DNA microarray and suppressive subtractive hybridization analyses show a global increase in hypoxia-activated genes.

Since both preeclampsia and IUGR are thought to share the same abnormality of placental implantation, namely, shallow placentation and hypoxia, contrasting their similarities and differences is useful for a better understanding each disorder.^{58,59} In early-onset IUGR, it is believed that the intervillous space and villous placenta are nonhypoxic or even relatively hyperoxic, with the hypoxia state being postplacental.⁵⁹ Although HIF protein expression has not been reported for these placentas, indirect evidence contradicts this notion. Insofar as soluble

sFlt-1 is regulated by hypoxia and HIFs, there is increased sFlt-1 expression in the placenta as well as increased maternal circulating levels of sFlt-1 in these pregnancies, suggesting a state of placental hypoxia, similar to that found in early-onset preeclampsia. In contrast, HIF levels and HIF-regulated genes are not increased in late-onset IUGR compared with late-onset preeclampsia, suggesting the lack of placental hypoxia.⁶⁰ The most likely explanation is that, in contrast to preeclampsia, uteroplacental oxygen delivery is matched to reduced placental and/or fetal oxygen consumption such that the placental intervillous PO₂ is not hypoxic. This conclusion is consistent with the finding that sFlt-1 is not increased in the maternal circulation of women with IUGR identified in late pregnancy.

Consequently, a noninvasive measurement of the relative state of placental oxygenation would be useful in the prediction, classification, and treatment of the obstetric diseases believed to be related to abnormal placentation. In this regard, noninvasive approaches such as near-infrared spectroscopy and blood oxygen level-dependent magnetic resonance imaging may prove to be safe and reliable methodologies.^{61,62} When relative placental ischemia/hypoxia is a component of the disease, strategies to improve uteroplacental blood flow may be beneficial to improve placental and fetal growth and/or alleviate maternal endothelial dysfunction by reducing circulating toxic factors that emanate from the placenta as a consequence of local hypoxia. In this regard, recombinant human relaxin may be efficacious not only by improving maternal renal and systemic hemodynamics (without causing undue systemic hypotension) but also by vasodilating unremodeled spiral arteries and more proximal, vasoconstricted uterine arteries.⁶³

The prepregnancy phenotype. Preexisting maternal conditions, such as obesity and insulin resistance, may interact with placental factors to predispose women to develop preeclampsia. There is evidence consistent with the hypothesis that lifelong predisposition to inflammation and endothelial dysfunction, particularly evident in women with obesity and the insulin resistance syndrome, becomes unmasked during the metabolic stress of pregnancy and precipitates the preeclampsia syndrome. In this context, pregnancy per se can be considered a stress test of maternal lipid, carbohydrate, and inflammatory pathways.⁶⁴

Maternal obesity is the major modifiable risk factor resulting in the translation of abnormal placentation into the maternal preeclampsia syndrome. Two recent

investigations of the relation between maternal prepregnancy body mass index (BMI) and the risk of severe and mild subclassifications of preeclampsia have revealed a steep dose-response relation between prepregnancy BMI, throughout the BMI distribution, and risk of both mild and severe (including preterm) preeclampsia.^{65,66} A large, prospective, population-based study recently showed that weight gain during the interpregnancy interval is strongly associated with the risk of major maternal and perinatal complications, including preeclampsia, independent of whether women are overweight.⁶⁷ The mechanisms by which increasing adiposity predisposes to preeclampsia are unclear. It is also unknown why, even with a 3-fold increased risk, more than 90% of women with prepregnancy obesity will not develop the disease.

The same underlying maternal metabolic disturbances that may contribute to preeclampsia may also increase a woman's risk of developing cardiovascular disease later in life.⁶⁴ The increase in cardiovascular-related mortality becomes evident about 20 years after delivery in groups of women with a history of nonrecurrent preeclampsia, later than women with a history of recurrent preeclampsia.⁶⁸ Obesity and related insulin resistance, dyslipidemia, and low-grade chronic inflammation are key determinates to understanding the relationship of preeclampsia and later cardiovascular disease.^{64,69} Interventions that have been successful in preventing atherosclerosis, including tight glucose control, prepregnancy weight control, and exercise, deserve further study for the prevention of preeclampsia. Women with a history of preeclampsia may benefit from early surveillance and aggressive prevention strategies. Among these women, there should be increased emphasis on evaluating whether postpartum lifestyle interventions can attenuate both risk for morbidity in subsequent pregnancies and later cardiovascular disease.⁶⁴

Angiogenic factors. Imbalance of angiogenic growth factors in the maternal circulation may underlie the pathogenesis of preeclampsia. Placental production of sFlt-1, an endogenous antiangiogenic protein that antagonizes VEGF and placental growth factor (PlGF), appears to be a central player in this paradigm.⁷⁰ In vitro studies indicate that excess placental sFlt-1 production induces an antiangiogenic state in the serum of preeclamptic women that can be rescued by exogenous VEGF and PlGF. Exogenous gene transfer of sFlt-1 into pregnant rats using an adenoviral vector produced hypertension, proteinuria, and glomerular endotheliosis, the classical

pathological renal lesion of preeclampsia. High serum sFlt-1 and low serum-free PlGF and free VEGF have been observed in the disease and, importantly, antedate clinical symptoms by several weeks.¹⁹

Another potential soluble factor secreted by the placenta that appears to be elevated in women with preeclampsia is soluble endoglin (sEng).²⁰ Endoglin (Eng) is an angiogenic receptor expressed mainly on the surface of endothelial cells but also placental syncytiotrophoblasts. Eng acts as a co-receptor for transforming growth factor- β , a potent proangiogenic molecule signaling in endothelial cells. In contrast to sFlt-1, sEng is not derived from alternative mRNA splicing but rather by proteolytic cleavage of the extracellular region of the Eng protein. Eng mRNA is upregulated in the preeclamptic placenta, and preeclamptic women release excess quantities of sEng protein into the circulation. Furthermore, in animal experiments, sEng appeared to exacerbate the vascular damage mediated by sFlt-1 in pregnant rats, resulting in severe preeclampsia-like illness including the development of hemolysis, elevated liver enzyme levels, and a low platelet count (HELLP) syndrome as well as fetal growth restriction.⁷¹

What remains unknown is the origin of the increased sFlt-1 and sEng in preeclamptic patients and whether these markers can be used for the diagnosis and prediction of the disease. Interventions targeting sFlt1 and sEng may prove to be novel therapeutic strategies for both its prevention and treatment.

Genetics. Preeclampsia has a significant genetic component.⁷² It is best considered a complex disease with a polygenic inheritance pattern and subject to strong environmental effects. Significant phenotypic heterogeneity is likely due to ethnic, clinical, locus, allelic, epigenetic, and environmental differences between individuals. Furthermore, pleiotropy (1 gene leading to many actions) can also be observed, which can also increase the complexity of a genetic analysis because of multiple effects on the phenotype of a single mutant gene. For instance, women who carry the angiotensinogen threonine 235 mutation have a higher frequency of not only preeclampsia but also of abruptio, IUGR, and idiopathic preterm labor.⁷³

There are many challenges in genetic studies of preeclampsia.^{21,74} The trait is gender limited with a late pregnancy-limited expression. The definition of the phenotype may not correlate closely with the underlying genotypes. The full expression of the disease gene can be interrupted by appropriate medical care or early delivery.

Alleles must be extremely common, and a large percentage of cases are likely to be due to new mutations. The genotype of the mother, the fetus, or an interaction between the two may also be critical in disease manifestation. Several predictions can be made with respect to preeclampsia genes: Hundreds of genes will likely be involved because of evolutionary redundancy to ensure successful reproduction. Ethnic variation will be extreme because of hyperevolution of the human placenta. New mutations/different mutations will be common based on the high frequency of perinatal lethality. Major protective alleles will be involved because of their strong selection. Monogenic and common polygenic forms will be rare. Animal models will have limited utility because of evolutionary divergence.

Unfortunately, linkage studies have been plagued by low power, an incorrect model of inheritance, and heterogeneity creating false pedigrees, while genetic association studies have suffered from low power, lack of replication or biologic validation, and ethnic biases. Fortunately, the information contained in the human genome is finite. Given the powerful tools now available, a comprehensive understanding of the genetics of preeclampsia is within reach. The ability to characterize patients by their underlying predispositions should enhance most research methods used to study this common and morbid pregnancy complication.

Thrombophilia. During the past 2 decades, several observational, case-control, and prospective observational studies have evaluated the association between thrombophilias and preeclampsia. Moreover, the association between thrombophilia and preeclampsia has been the subject of several reviews and meta-analyses.^{75,76} Overall, the results of published reports have been inconsistent. In women with severe preeclampsia, the reported incidence of protein S deficiency ranged from 5% to 25%. The incidence of Factor V Leiden mutation was 4.5% to 26% and that of prothrombin gene mutation was 0% to 9.1%.⁷⁵ The reason for the differences in findings among various studies relates to the heterogeneous group of patients studied. Almost all studies were performed in complicated or severe cases of preeclampsia that were referred to tertiary care obstetric units, and most studies used term-normal pregnancies as the control group.

Recently, Mello et al⁷⁷ reported the results of a large, multicenter, case-control study comparing the frequency of thrombophilia between white Italian women with preeclampsia and those with term-normal pregnancies. A

strong association was found between thrombophilia and severe preeclampsia but not with mild preeclampsia. There are few case series describing the prophylactic use of low-molecular-weight heparin with or without low-dose aspirin in women with genetic thrombophilia and a previous history of adverse pregnancy outcome including severe preeclampsia and/or fetal growth restriction.^{75,78} All these studies were observational, comparing the outcome in treated pregnancy to that of a previously untreated pregnancy in the same patient.⁷⁵

Further research is required to determine the role of thrombophilias in the pathogenesis of preeclampsia and to determine which women with severe preeclampsia should be screened for thrombophilias. These studies should address gestational age at onset, race and ethnicity, and the presence or absence of associated medical and obstetric complications. Moreover, they should answer questions regarding what laboratory tests to obtain and what test result is considered abnormal. Finally, there is a need for randomized controlled trials of thromboprophylaxis therapy versus placebo for the prevention of recurrent preeclampsia in women with thrombophilia and a history of preeclampsia.

Dietary factors. Consistent with the increased risk experienced by overweight women is the long-standing belief that preeclampsia is related to the maternal diet.⁷⁹ During World Wars I and II, reduced risks of eclampsia, gestational hypertension, and preeclampsia were observed among European women in association with food shortages and famine. More than 2 decades ago, it was observed that African American women from Tuskegee who developed preeclampsia had diets that were rich in fat.⁸⁰ Over the years, the evolution of theories about nutrition and preeclampsia led obstetricians, dietitians, and other providers to give well-intentioned dietary advice that led women with preeclampsia to change what they ate. This, in conjunction with the retrospective nature of most of research, may have distorted relationships with the maternal diet.

In later life, women with preeclampsia during pregnancy have an increased risk of cardiovascular disease. Consequently, it seems plausible that diet could be involved in the etiology of preeclampsia, as it is in cardiovascular disease. However, there are few prospective studies. Dietary data from a large clinical trial (Calcium for Preeclampsia Prevention Study) that used a single 24-hour recall and combined nutrients from a multivitamin with intake suggested no association between any of the 23 nutrients measured and preeclampsia.⁸¹ Nutrients or biomarkers of diet that have been studied prospectively

or in clinical trials include the following: omega-3 fatty acids and other fats, calcium, the dietary antioxidants vitamins C and E, circulating levels of homocysteine (regulated by folate and the B vitamins), and the use of multivitamin/mineral supplements by pregnant women.^{82,83} The long-term sequelae of preeclampsia on women's cardiovascular health need to be further studied.

Prediction of Preeclampsia

Role of Doppler. The assumptions behind the use of uterine arteries (UtA) Doppler during the midtrimester for prediction of preeclampsia are that (1) the disease is predominantly secondary to failed conversion of the spiral arteries due to abnormal trophoblastic invasion in the myometrium, (2) conversion of the spiral arteries is essentially completed by 20 to 24 weeks, and (3) assessment of impedance to flow in the UtA reflects downstream changes in spiral arteries. In addition, preeclampsia is a pathogenically heterogeneous condition with a continuum of onset and severity. Fortunately, the pregnancy complications best predicted by UtA Doppler are those of greatest clinical risk, such as preeclampsia manifesting preterm or pregnancies complicated by fetal growth restriction or placental abruption.⁸⁴⁻⁸⁶ In addition, conversion of the spiral arteries is an ongoing process, so that the predictive ability of UtA Doppler improves greatly with advancing gestational age up to 28 weeks. Moreover, UtA Doppler results have only limited correlation with histology of the placental bed, probably because of geographical variations in the sampled tissues and because placental bed biopsies may not be representative of the entire placental pathology. Midtrimester UtA Doppler is also an inadequate screening test for preeclampsia because it has a moderate to minimal level of prediction of any degree of severity of preeclampsia both in low-risk and high-risk patients when the test is performed at 20 to 24 weeks, and no adequate prophylaxis to prevent preeclampsia has been identified for women at risk for the condition based on UtA Doppler.⁸⁷

There are a number of areas requiring research for the effective use of UtA Doppler in preeclampsia. These include use of UtA Doppler for prediction of complicated preeclampsia rather than any type of preeclampsia; adoption of formulas that take advantage of the quadratic relationship between the results of UtA Doppler indices and the risk of complicated preeclampsia (rather than dichotomizing results into normal and abnormal), allowing individualized calculation of risk for complicated preeclampsia⁸⁶; addition of serum markers to UtA Doppler

(particularly at the end of the first trimester) to enhance the predictive ability of UtA Doppler alone; evaluation of the benefit of prophylaxis begun in the first trimester in women identified as at risk for preeclampsia by such combined screen⁸⁸; and assessment of the cost-benefit ratios of UtA Doppler screening (eg, implementation of intensive surveillance in low-risk women with abnormal results and avoidance of such measures in high-risk women with normal results).

Measurement of angiogenic factors. The maternal hypertensive syndrome of preeclampsia may be caused by an antiangiogenic state in the blood, characterized by high levels of the antiangiogenic proteins sFlt1 and sEng and low levels of the proangiogenic proteins free PlGF and free VEGF.^{19,20} Evidence for causality is accumulating and includes a strong association with preeclampsia, a time sequence consistent with causality, dose-response relationships, biological plausibility, and disease susceptibility.^{19,20,89-91} If abnormalities in angiogenic proteins do comprise the final common pathway to the maternal syndrome, measurement of concentrations of angiogenic proteins in blood or urine may also be useful for predicting the onset and severity of preeclampsia, for the diagnosis of preeclampsia, and for distinguishing preeclampsia from conditions that may mimic it, including chronic hypertension, chronic renal disease, and epilepsy.⁹²

Further research is required to substantiate and enhance the value of angiogenic factors for the prediction and diagnosis of preeclampsia. This should include (1) measurements of angiogenic factors by week of gestation in large populations of pregnant women without manifestations of preeclampsia or gestational hypertension to define a reference range, (2) longitudinal measurements in low-risk and high-risk women before and after the onset of preeclampsia to develop and test prediction models, and (3) the development of rapid, reliable assays for use in the clinical setting. Moreover, research on the possible relationship of angiogenic factors to the well-known risk factors for preeclampsia may also be important to explain the effect of chronic hypertension, diabetes, multifetal gestation, BMI, midtrimester blood pressure, parity, age, race, and smoking on preeclampsia risk.

Prevention Trials

What has been learned. More than 45 000 subjects have been studied in trials to assess the benefit of antiplatelet agents (usually aspirin) or calcium in reducing preeclampsia

risk.^{93,94} At this juncture, one must ask what scientific information has been gleaned from these studies. Clearly, in the United States, neither low-dose aspirin nor calcium is routinely used for preeclampsia prevention.

One can view these results in several ways. First, one can say with some degree of confidence that the public has been protected from ineffective and unnecessary treatments. Another perspective might be that money and resources have not been used wisely and that we should question whether these resources could have had a greater impact if a greater number of small mechanistic trials, cohort studies, or basic research studies were undertaken, thus avoiding the need for large, randomized clinical trials (RCTs). The sample size required to demonstrate an effect size of 10% is affected by the prevalence of disease. For example, about 70 000 women would need to be randomized to demonstrate a benefit of such therapy for a treatment effect of 10% if the preeclampsia prevalence is 4% (as is the case with uncomplicated women). With low-prevalence diseases, it may be best to define high-risk populations using a cohort or small explanatory studies.

It is clear that the impetus for most large, multicenter RCTs stems from small clinical trials showing a benefit of intervention. The challenge facing the scientific community is how best to address the findings of small positive trials. Should a multicenter RCT be the first choice, or should small explanatory RCTs delving into the mechanism of disease be undertaken first? What role can cohort studies play in such circumstances? Should additional basic science studies be performed before any randomized clinical trial is undertaken? The advantages of RCTs are clear. An RCT is the best way to evaluate the utility of a given treatment. RCTs provide unbiased prevalence data and minimize the impact of variations inherent in populations. RCTs, however, have many disadvantages. They are costly and require a large sample size because many of the groups at greatest risk for the outcome of interest are excluded while subjects at low risk are included. An RCT, if negative, does not exclude a benefit in some subset of patients if not adequately powered, resulting in the inability to answer the scientific question that led to the RCT. Ideally, before undertaking an RCT, there should be overwhelming scientific evidence supporting the biological probability for a given intervention. The group that can best benefit from treatment needs to be clearly defined; otherwise, low-risk patients are recruited into the trial, diluting out the treatment effect. The prevalence of disease in the population

to be studied should be defined by cohort studies or by retrospective analysis of the participating institution's database using strict disease definitions. Effect size estimates for an RCT should be based on meta-analysis or data from multiple small studies. When pharmacologic treatments are used in RCTs, it is necessary to obtain pharmacokinetic data to ensure proper dosing and to define biological variation. Likewise, pharmacodynamic assessment is needed to show that the treatment affects or remedies the biological aberration associated with or causing the disease. Given the current circumstances in preeclampsia research, with multiple failed interventions, clearly more basic research and small explanatory clinical studies are needed to define potential mechanisms of disease and therapy.

Oxidative stress and the theoretical basis for trials. Oxidative stress appears to be a universal feature of both maternal and fetal tissue in preeclampsia.⁹⁵ Oxidative stress can be a physiologic regulator in certain situations in the placenta (eg, the process of trophoblast invasion). Pregnancy per se is a state of oxidative stress due to the high metabolic activity of placental mitochondria and resultant generation of reactive oxygen species (ROS). Oxidative stress may be the principal process that gives rise to the vascular dysfunction of preeclampsia. The fatty acid and cytokine profile of obese diabetic or preeclamptic women favors oxidative stress, which may provide a link between these conditions and increased risk for development of preeclampsia.

Sources of ROS generation include the enzymes xanthine oxidase and NADP(H) oxidase (NOX). Both placental vascular endothelium and trophoblast express both NOX-1 and NOX-5 isoforms and are significantly increased in all placental cell types from pregnancies complicated by preeclampsia including early- and late-onset disease.⁹⁶ Expression of the NOX enzymes may be upregulated by ischemia/reperfusion or hypoxia but also by inflammatory cytokines. The placenta and vascular endothelium also produce reactive nitrogen species including nitric oxide (NO). ROS and NO interact to produce peroxynitrite. Peroxynitrate is a powerful pro-oxidant that nitrates tyrosine residues on proteins. This covalent modification can result in altering a protein's function. Nitrotyrosine residues are found in the placenta and the maternal vasculature, showing perhaps a generalized incidence of nitrative stress in preeclampsia.⁹⁷ As individuals with preeclampsia have reduced concentrations of vitamin C and E prior to the disease, an empiric therapy would be antioxidant supplementation.⁹⁸ Moreover,

the time of administration relative to placental (early) or maternal vascular (later) involvement in generation of preeclampsia would be critical. Therefore, early administration of antioxidant supplementation may be beneficial not only for trophoblastic events but also vascular events.

The Vitamins in Preeclampsia Trial. In a previous small study of women at risk of preeclampsia, with the primary outcome being a reduction in maternal concentrations of biomarkers of preeclampsia, it was shown that supplementation with vitamins C and E led to a significant improvement in the primary outcome (ie, a ratio of plasminogen-activator inhibitor of 1:2).¹¹ The rate of preeclampsia, a secondary outcome, was also reduced. Based on the promising findings of this study, a much larger placebo-controlled trial study was initiated called Vitamins in Preeclampsia Trial (VIP).¹² A total of 2410 at-risk women were enrolled from 25 hospitals and randomized to either daily vitamins C and E therapy (1000 mg vitamin C and 400 IU vitamin E) or placebo. The inclusion criteria were women with 1 or more preeclampsia risk factors between the gestational ages of 14 to <21 weeks. The primary end point was preeclampsia, and the main secondary end points were low birth weight (<2.5 kg) and small size for gestational age (<fifth centile for customized birth weight). Analyses were by intention to treat. Of 2404 patients treated, 2395 were analyzed. The incidence of preeclampsia was similar in treatment and placebo groups (15% vs 16%, respectively; relative risk [RR], 0.97; 95% confidence interval [CI], 0.80-1.17). More low-birth-weight babies were born to women who took antioxidants than to controls (28% vs 24%; RR, 1.15; CI, 1.02-1.30), but small size for gestational age did not differ between groups (21% vs 19%; RR, 1.12; CI, 0.96-1.31). This study has clearly shown that supplementation with antioxidant vitamins C and E starting in the second trimester in women at risk for preeclampsia on the basis of recognized clinical criteria does not prevent the disease.

The Australian Collaborative Trial of Supplements. The Australian Collaborative Trial of Supplements (ACTS) with vitamin C and vitamin E assessed whether supplementation reduced perinatal complications in nulliparous women.¹³ A total of 1877 nulliparous women with a singleton pregnancy between 14 and 22 weeks' gestation with a normal blood pressure were enrolled in the study; 935 women were randomly assigned to daily vitamin therapy (1000 mg vitamin C and 400 IU vitamin E), and 942 women were assigned to the placebo group.

There were no significant differences between the vitamin and placebo groups for the risk of preeclampsia (6.0% vs 5.0%, respectively; RR, 1.20; CI, 0.82-1.75), the risk of death or serious outcome for infants (9.5% vs 12.1%; RR, 0.79; CI, 0.61-1.02), or the risk of having an infant with a birth weight less than the 10th centile for gestational age (8.7% vs 9.9%; RR, 0.87; CI, 0.66-1.16). Significantly fewer infants in the vitamin group had respiratory distress syndrome and required the use of surfactant. Women in the vitamin group had an increased risk of being admitted antenatally for hypertension, being prescribed antihypertensive drugs, and of having raised aminotransaminases.

In the ACTS, supplementing healthy nulliparous women with 1000 mg vitamin C and 400 IU vitamin E daily during pregnancy did not reduce their risk of developing preeclampsia, the risk of serious outcome for their infant, or the risk of IUGR. These results do not support routine vitamin C and E supplementation to prevent preeclampsia or other adverse pregnancy outcomes in nulliparous women.

The Combined Antioxidant and Preeclampsia Prediction Study. The ongoing Combined Antioxidant and Preeclampsia Prediction Study (CAPPS) was initiated in 2003. The study is an RCT designed to test the safety and efficacy of antioxidant vitamins C (1000 mg) and E (400 IU) to prevent the adverse outcomes of preeclampsia. The study is composed of 10000 low-risk primiparous women, and the primary outcome is adverse outcomes associated with the condition rather than the incidence of preeclampsia. In addition, this study includes an observational prediction component in which biologic specimens are obtained from a subset of women throughout pregnancy.

The CAPPS study begins therapy at 8 to 16 weeks, with 40% entering at less than 12 weeks, which differs from the VIP and ACTS trials, with an average gestational age of randomization at 18 weeks in both groups. The major oxidative stress accompanying the formation of the intervillous circulation at 9- to 10-week gestation suggests benefit for earlier therapy. However, whether earlier treatment will result in different results remains to be seen. Of major importance, the prediction component may provide information on the differences in subsets of women who do or do not benefit from therapy. It will also indicate the changes in pathophysiology, including whether oxidative stress was abated.

Management

New therapies of preeclampsia. The main objective of the management of preeclampsia is the safety of the mother.⁹⁹ Although delivery is always appropriate for the mother, it might not be best for a very premature fetus. After diagnosis, subsequent treatment will depend on the results of initial maternal and fetal assessment.³ The decision between delivery and expectant management depends on fetal gestational age, fetal status, and severity of maternal condition at time of assessment. This objective can be achieved by formulating a management plan that considers 1 or more of the following: fetal gestational age, maternal and fetal status at the time of initial assessment, presence of labor, or rupture of fetal membranes.^{99,100}

Some of the traditional managements of preeclampsia have included 1 or more of the following: complete or partial bed rest for the remainder of pregnancy, antihypertensive therapy to prolong pregnancy, close maternal-fetal surveillance, and delivery at or near term. During the past decade, several investigators have reported on the use of various therapies to improve the perinatal outcome in women with severe preeclampsia.^{101,102} These included corticosteroids for fetal lung maturity and/or to improve maternal outcome in HELLP syndrome, plasma volume expansion, and expectant management in a select group of women with severe preeclampsia. These therapies have demonstrated some temporary perinatal benefits for at least 48 hours, but their safety remains unproven. Many challenges remain regarding the management of the disease, particularly those developing before 34 weeks' gestation.

Future research should expand our knowledge to identify new target molecules and diagnostic biomarkers in such women, which will ultimately aid in formulating targeted interventions to improve pregnancy outcome in patients with severe preeclampsia remote from term. Finally, there is a need for randomized controlled trials to test new interventions that are designed to prolong gestation and improve perinatal outcome in cases of preeclampsia that are usually associated with adverse maternal and perinatal outcomes.

RESEARCH GAPS AND FUTURE DIRECTION

It was the overall consensus that the pathophysiological underpinnings of preeclampsia are not solely vascular, genetic, immunologic, or environmental but a complex combination of factors. Furthermore, preeclampsia (at least

early onset) should be considered to evolve in 2 stages. The first stage (<20 weeks of gestation) comprises poor placentation, at which time there are no signs or symptoms of the disease. The second stage (>20 weeks of gestation) comprises the downstream consequences of poor placentation, probably associated with hypoxia with or without ischemia-reperfusion injury, which damages the syncytium, limits fetal growth, and leads to the clinically evident disease. In addition, a number of scientific gaps were identified in the following areas.

Multidisciplinary and Collaborative Research

- Increased collaboration between researchers is required that brings together different techniques and disciplines into more comprehensive and cohesive projects. For example, studies are needed that couple molecular and morphometric data with structural changes.
- Collaboration between basic and clinical researchers is needed for the design and implementation of more effective research protocols. For example, the basic researcher generally has a better knowledge of newer approaches (eg, technological, mathematical, etc) to old problems, while the clinical researcher may have better insight into the clinical relevance of the approach(s).
- More research is required that embraces powerful data-generating approaches, such as the use of genomic, proteomic, and metabolomic high-throughput platforms. In this regard, multidisciplinary studies melding molecular, clinical, and epidemiological study designs are also required.
- More international research collaboration is necessary, especially in the context of the limited resources available. International collaboration in preeclampsia research should be a unified effort, as the numbers of research groups is small and resources are limited. It was suggested that a large, international, prospective study should be undertaken to better understand the pathophysiology of the disease. This prospective study should have well-defined end points using meticulous protocols for the collection of clinical data and specimens.
- Research collaboration with the pharmaceutical industry should be encouraged to develop novel therapeutic strategies to ameliorate and/or prevent preeclampsia.

Clinical Trials and Patient Management

- Ideally, large clinical trials are best designed by a firm understanding of the underlying pathophysiology of

the disease to best formulate an effective intervention. Practically, most large clinical trials are based on promising small pilot studies of therapy, which are supported by mechanistic and observational (association) studies, because of the urgent need for an effective intervention. The recent disappointment of the 2 large clinical trials of antioxidants indicates that even strong evidence of association and pilot data suggesting efficacy may not necessarily avoid unsuccessful trials. A useful adjunct may be the use of small trials that use not the prevention of disease as the outcome but rather a more sensitive end point, such as mechanistic modifications. Nonetheless, a careful evaluation should be made before an intervention is tested based on causality, biological plausibility, and promising results of small pilot studies. Furthermore, any large RCT should include a mechanistic component to identify subsets of responders or nonresponders and to provide data for future interventions.

- Future interventions should be started earlier in pregnancy compared with many past clinical trials. Since poor placentation is probably the proximate cause of early-onset preeclampsia, it is likely that a clinical intervention would be most effective if started during the period of the vascular remodeling of the maternal-fetal interface (8–16 weeks of gestation).
- Until there are proven interventions to prevent preeclampsia, there is a need for research in the screening and management of the disease, with the goal of affecting health outcomes. Once effective screening and management regimens are established, then research can be extended using these regimens for recurrence of the disease.
- Health services research strategies should be used to establish methods to facilitate the rapid and widespread adoption of practice management based on current and future knowledge.

Specific Research Areas

- Attempts should be made to identify subsets of the disorder that may have different pathophysiologies. The differences in outcome in the first pregnancy versus recurrent preeclampsia mandate that investigators study preeclampsia in primiparas and multiparas separately. In addition, delineation between early onset and late onset of disease is important; because they are based on available observational data, they are also likely to be associated with different pathophysiologies. Furthermore, research should be more focused on preeclampsia occurring early in pregnancy as this is often associated with severe disease.

- A uniform definition of preeclampsia is required. Preeclampsia could be better defined by including other measures that are abnormal, besides blood pressure and proteinuria, such as sFlt-1 and uric acid levels. There is also a need to study defined subtypes according to the time of onset of the disease.
- More emphasis on the study of normal maternal adaptations to pregnancy and normal placentation is required to better understand the pathophysiology of preeclampsia.
- More research studies using selected primates, with placentation similar to humans, is needed to better understand the role of impaired placentation in the pathogenesis of preeclampsia.

SUMMARY

Progress is being made in understanding the possible factors involved in preeclampsia, albeit not as rapidly as one would desire. A number of important research gaps were identified by the workshop participants. The challenge is to better understand the disease to reach the ultimate goal of effective interventions that can prevent the disease or, at the least, lead to interventions that can ameliorate its detrimental effects. In the meantime, attempts should be made to optimize therapy through health services research directed at determining how the care provider and patient can most effectively recognize and manage the disorder. We hope that this article will aid the research community in attaining these goals.

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