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REPORT of the WORKING GROUP on RESEARCH on HYPERTENSION DURING PREGNANCY

Meeting Held April 27, 2001
National Heart, Lung, and Blood Institute

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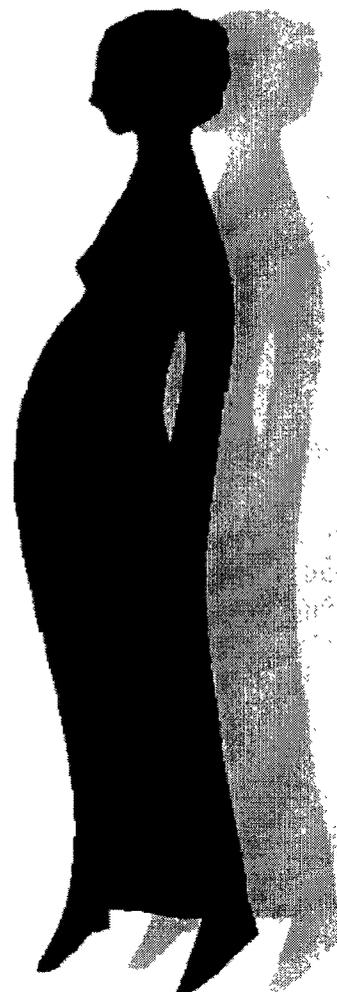
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BACKGROUND

Hypertensive disorders of pregnancy, which affect an estimated five to eight percent of pregnancies in the United States, contribute significantly to serious complications for both the fetus and the mother. An important distinction exists between the preeclampsia syndrome, recognized when elevated blood pressure occurs for the first time during pregnancy, and preexisting (chronic) hypertension. The two disorders, although both characterized by high blood pressure, are strikingly different pathophysiologically and have very different acute and long-range implications for mother and infant. Gestational hypertension and preeclampsia superimposed on chronic hypertension are also discussed in the "Definitions" section.

Preeclampsia is the most common hypertensive disorder during pregnancy, affecting an estimated 5-8% of pregnant women annually in the United States, and has the greatest effect on maternal and infant outcome. Chronic hypertension affects an increasing proportion of pregnancies, and confers significant risk for the development of preeclampsia. Preeclampsia occurs more frequently and is more severe in women with preexisting hypertension than in women who are normotensive prior to pregnancy. From a public health perspective, it is alarming that the rate of preeclampsia has increased by nearly one-third over the past decade, likely due to a rise in the number of older mothers and multiple births, scenarios that predispose to preeclampsia. Older maternal age during pregnancy also contributes to an increased frequency of chronic hypertension and thus preeclampsia complicating pregnancy.



Maternal complications acutely can include pulmonary edema, thrombotic complications, renal failure, and death. Preeclampsia can evolve into eclampsia, leading to maternal seizures. One specific subset of signs and symptoms known as the HELLP Syndrome (Hemolysis, Elevated Liver Enzymes, and Low Platelets) is a cause of extensive morbidity. In the United States, hypertensive disorders of pregnancy account for nearly 15 percent of maternal mortality; throughout the world these conditions are responsible for more than a third of maternal deaths. The vast majority of these deaths and most infant deaths are due to preeclampsia and eclampsia, arising either *de novo* or superimposed on chronic hypertension. Long-term sequelae may also result. Women with chronic hypertension have an obvious long-term risk from the persistent hypertension. However, women with preeclampsia, despite the resolution of the disorder postpartum, are also at increased risk of cardiovascular disease in later life compared to women with pregnancies without preeclampsia.

Fetal complications of hypertensive disorders of pregnancy include growth restriction, prematurity, and stillbirth. In addition, there is evidence that the intrauterine milieu in a hypertensive pregnancy may, by mechanisms related to the failure of the fetus to exercise full growth potential, confer increased risk of cardiovascular events in adult life.

Two millennia ago, Celsus described puerperal seizures, termed eclampsia. In the late 19th century, it was recognized that increased blood pressure and proteinuria preceded the seizures. Soon thereafter, physicians realized that these findings constituted the syndrome of preeclampsia, which increased maternal and infant mortality and morbidity even if seizures did not occur. Over the past decade, a great deal of attention has been focused on understanding the pathophysiology of preeclampsia to assist in devising therapeutic interventions for subsequent assessment. This has resulted in a better understanding of the pathophysiological mechanisms, but many details remain unclear. In addition, clinical trials testing two promising therapies, calcium supplementation and aspirin, to prevent preeclampsia or improve its outcome, demonstrated at most minor benefits. Progress has been limited by the lack of animal models with placental physiology comparable to humans. In contrast to preeclampsia, in chronic hypertension where prior knowledge of pathophysiology of the disease in nonpregnant women provides useful insight to treatment, little work has been done to apply these insights to therapy for women with hypertension who become pregnant.

Because of the clear public health concerns engendered by hypertensive disorders of pregnancy, and the urgency of providing new directions in research, the National Heart, Lung, and Blood Institute (NHLBI), with input from the National Institute of Child Health and Human Development (NICHD) convened a Working Group on Research on Hypertension During Pregnancy. The Working Group was charged with evaluating the current state-of-the-science and making recommendations for a focused basic, clinical and translational research agenda addressing key issues in pregnancy-related hypertension. The current Working Group was constituted in part to have overlap with the Working Group that produced the National High Blood Pressure Education Program's (NHBPEP/NHLBI) recent Working Group Report on High Blood Pressure in Pregnancy (Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, *Am J Obstet Gynecol* 2000;183:S1-S22). The current Working Group was expected to build on this Report, as well as to use other sources of data and personal expertise to advise the Institute on research priorities in a variety of areas, such as epidemiological studies, clinical trials, mechanistic research on the pathophysiology of the various forms of high blood pressure during pregnancy, and training.

DEFINITIONS

Hypertension during pregnancy is categorized as: preeclampsia/eclampsia, gestational hypertension, the continued presence of chronic hypertension, and preeclampsia superimposed upon chronic hypertension. These categories identify disorders with different epidemiological characteristics, pathophysiology, and risk for mother and baby.

- **Preeclampsia** is defined as a pregnancy-specific syndrome observed after the 20th week of pregnancy with systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mmHg, accompanied by significant proteinuria. Previous definitions included edema as part of the diagnosis, but this has subsequently been dropped as being too non-specific. Likewise, the criteria of a 30-point change in systolic blood pressure or a 15-point change in diastolic blood pressure have been eliminated for the same reason in favor of an absolute blood pressure threshold. As proteinuria may be a late manifestation, the NHBPEP also advises clinicians that the disease should be suspected if high blood pressure is accompanied by symptoms of headache or abdominal pain, or abnormal laboratory tests, specifically low platelet count and abnormal liver enzymes. In women with preeclampsia, blood pressure usually returns to baseline within days to weeks after delivery.
- **Eclampsia** is the occurrence, in a woman with preeclampsia, of seizures that cannot be attributed to other causes. Convulsions usually occur after midpregnancy, and may occur postpartum.
- **Gestational hypertension** is defined as a blood pressure elevation detected for the first time after midpregnancy, and is distinguished from preeclampsia by the absence of proteinuria. The category of gestational hypertension is a nonspecific working diagnosis, which includes women who will proceed to satisfy diagnostic criteria for preeclampsia, as well as those who never develop proteinuria and whose blood pressure returns to baseline following pregnancy and women with increased blood pressure prior to pregnancy masked by the tendency of blood pressure to decrease in early pregnancy. Gestational hypertension is a working diagnosis only during pregnancy. If proteinuria develops and the hypertension resolves after the pregnancy, the diagnosis is changed to preeclampsia. If elevated blood pressure persists, chronic hypertension is diagnosed. In the absence of other factors, the diagnosis is termed transient hypertension of pregnancy.
- **Chronic hypertension** refers to an elevated blood pressure in the mother that predated the pregnancy. It can also be diagnosed in retrospect, when preeclampsia or gestational hypertension fail to normalize after delivery. Chronic hypertension in the mother may not have been recognized prior to the pregnancy, and may not be under medical control. At present, there are few therapeutic alternatives for treating pregnant women with preexisting hypertension. This is particularly important because women with chronic hypertension are at increased risk of **superimposed preeclampsia** (25% risk), preterm delivery, fetal growth restriction or demise, abruptio placentae, congestive heart failure and renal failure. The outcome for mother and infant is worse than for de novo preeclampsia. It is unknown how treatment of chronic hypertension affects the risk of preeclampsia and its complications.

STATE-OF-THE-SCIENCE

Preeclampsia was the focus of most of the Working Group's discussion because it is the most common of the hypertensive disorders of pregnancy, and is associated with the highest rate of acute maternal and infant mortality and morbidity. However, issues concerning chronic hypertension in pregnancy also received attention primarily because of clinical concerns about the lack of evidence-based recommendations for treatment.

Today, the pathophysiology of preeclampsia is increasingly well-understood, but the etiology, early predictive markers, and means of effective prevention remain elusive. Preeclampsia is a pregnancy-specific syndrome in which there is increased vascular responsiveness to vasoconstrictor stimuli and activation of the coagulation cascade. The initial insult appears to be reduced placental perfusion frequently due to abnormal implantation of the blastocyst and abnormal remodeling of the maternal vessels that supply the intervillous space. These phenomena lead to decreased perfusion of the placenta and are considered by some to represent stage one of a two-stage process. Stage two refers to development of the maternal and fetal syndrome of preeclampsia. At present, the link between stages is not clear. It is evident that

reduced placental perfusion does not always result in the maternal syndrome, and that maternal factors also are required. Genetic polymorphisms, fetal signals, and increased hypoxia at the maternal fetal interface likely play a role in the interaction of reduced placental perfusion and the maternal constitution to generate the preeclampsia syndrome. Many of these predisposing maternal factors are also risk factors for cardiovascular disease in later life. For example, coagulation abnormalities, dyslipidemia, increased inflammatory markers, and evidence of oxidative stress and endothelial activation are associated with increased cardiovascular disease risk, and also are detectable in women who develop preeclampsia, occurring before the overt clinical symptoms appear.

Areas of opportunity for research on hypertension during pregnancy were identified by the working group. A summary of key points in each of these areas follows:

Genetics. Differences in the frequency, timing, and severity of preeclampsia among populations, as well as evidence of heritability, suggest a role for genetic influence. The principal gap is in understanding the genetic heterogeneity that appears to be present. Genetic polymorphisms that may occur more frequently in preeclamptic women include angiotensinogen, Factor V Leiden, methylene tetrahydrofolate reductase, and lipoprotein lipase. These polymorphisms do not appear to be related to preeclampsia in all populations. Genome-wide search strategies are premature and would be compromised if they are based on retrospective diagnosis of preeclampsia from historical medical charts. Understanding the genetic diversity could lead to a role for pharmacogenetic research, as well as to identification of a subset of women with preeclampsia who may be at increased risk for cardiovascular disease in the future.

Hemodynamics. One of the barriers to advances in preeclampsia research is that the available knowledge about normal and abnormal hemodynamics in pregnancy is largely descriptive. Newer noninvasive techniques that measure components of the pulsatile arterial load including compliance, as well as techniques to assess markers of endothelial function, have only sporadically been applied in pregnancy. For example, very little is known about the hemodynamics of women with chronic hypertension who become pregnant. Because 25% of these women, compared to about 5% of non-hypertensive women, develop preeclampsia, this information should be obtained. Another need would be to characterize the hemodynamic parameters of women with type 1 and type 2 diabetes, who also are at increased risk of preeclampsia.

Immunology and Inflammatory Responses in Pregnancy and Preeclampsia. T-cell activation occurs in preeclampsia, and study of the maternal-fetal interface should provide additional information not only about normal pregnancy but also about pregnancies complicated by hypertensive disorders. Some women with preeclampsia also have autoimmune disorders. There are several promising animal models that suggest a role for inflammation in the pathogenesis of preeclampsia. There is evidence of activation of the inflammatory response in pregnancy that is further increased in preeclampsia. Researchers have thus been led to consider inflammatory markers both as important in the epidemiology of preeclampsia, and as a potential link between preeclampsia and future cardiovascular disease. For example, cytokines such as TNF-alpha are significantly increased in preeclampsia. Animal models may provide a means of testing hypotheses about inflammation, but because of differences in placentation across species, will not provide a definitive explanation of preeclampsia. Shedding of placental cells in the maternal circulation may also play a role in inducing inflammation. The surface of the placenta normally sheds, like skin, into the maternal circulation, a process stimulated by hypoxia and mediated by apoptosis.

Long-range Implications of Preeclampsia for Mother and Infant. Women with preeclampsia are at increased risk of cardiovascular disease compared to women who have pregnancies without preeclampsia. Epidemiological studies indicate that this likely is the result of common risk factors for preeclampsia and cardiovascular disease rather than preeclampsia causing cardiovascular

disease. Most of the risk factors for preeclampsia (e.g., race, dyslipidemia, obesity, diabetes, hypertension, and elevated homocysteine) are also risk factors for cardiovascular disease. Likewise, many of the pathophysiological features of preeclampsia (e.g., dyslipidemia, inflammatory and endothelial activation, insulin resistance) are features of cardiovascular disease. There is increasing evidence that women who have recovered from preeclamptic pregnancies manifest cardiovascular and metabolic differences compared to women who have had normal pregnancies. It is possible that the normal changes of pregnancy sensitize certain women to insults that would require years to manifest effects in the absence of pregnancy.

The long-term implications of preeclampsia for the offspring is another area about which little is known. Preeclampsia is associated with an increased risk of fetal growth retardation, but many children born to women with preeclampsia are appropriate for gestational age, and still others are large for gestational age. It is possible that the long-range outcome of even the growth restricted infants of preeclamptic infants is not the same as that of the usual growth-restricted infant.

Metabolism. Pregnancy is a hypermetabolic state, with cholesterol and triglyceride concentrations rising up to three-fold. In women with preeclampsia, these increases are further exaggerated. Conversely, homocysteine normally decreases in pregnancy, but the decrease is only half as great in preeclampsia. The coagulation cascade also is altered in pregnancy, and further deranged in preeclampsia. Many of the features of preeclampsia mimic the insulin resistance or metabolic syndrome, and insulin resistance is a prominent feature of preeclampsia. These findings provide evidence of a link between preeclampsia and future cardiovascular disease, although the direction of causation is unclear at present.

Nutrition/Physical Activity. Little information is available about diet and nutritional supplements and hypertensive disorders of pregnancy. Calcium supplementation has been reported to reduce the frequency of preeclampsia in South American populations with decreased calcium intake, but was not successful in a U.S. trial supported by NICHD and NHLBI. Further, standard tools for assessing nutritional status, such as food frequency questionnaires, have not been validated in pregnancy. Such instruments should be validated independently during each trimester of pregnancy as changes in standard serum biomarkers occur throughout gestation. Once validated, food frequency questionnaires in combination with serum markers, obtained prospectively, would minimize the inherent measurement errors of each and might identify specific populations at risk. Although physical activity is a well-known predictor of future cardiovascular risk, it has thus far received minimal attention in preeclampsia.

Oxidative Stress in Preeclampsia. An intriguing hypothesis is that the decreased placental perfusion characteristic of preeclampsia leads to placental hypoxia, that in conjunction with maternal constitution results in the generation of oxidative stress. The role of oxidative stress as the linkage of the two stages of preeclampsia is further supported by abundant evidence of oxidative stress in blood and tissues of women with preeclampsia. Furthermore, a small trial of antioxidant therapy (1,000 mg vitamin C and 400 IU of vitamin E) resulted in a reduced incidence of preeclampsia when begun at 22 weeks gestation in women at high risk for the syndrome. Thus, the closest thing to a treatment target in the field is anti-oxidant therapy based on this collection of hypotheses and data. However, effectiveness in large populations and, even more importantly, safety for the fetus, are not established.

Resources. Animal models are of limited benefit because of significant differences in placentation among mammals, as well as differences in length of gestation and perhaps even posture between mammalian models and humans. Animal models are useful for generation and testing of hypotheses, but it was agreed that definitive hypothesis-testing would require clinical studies in well-characterized populations of women before, during, and after pregnancy. It is currently assumed that cardiovascular differences between women who have had normal pregnancies and those who have had pregnancies complicated by preeclampsia indicate changes that antedated the pregnancy. This can only be differentiated from the alternative explanations that these are

residual effects of preeclampsia or that normal pregnancy has a long-term beneficial cardiovascular effect by data accumulated in a subset of women prior to a preeclamptic pregnancy. Normative data on placental vascular biology and on hemodynamic alterations in pregnancy are also required as a baseline for subsequent study of alterations due to preeclampsia. Many hypotheses about prevention and future cardiovascular risk require longitudinal cohort studies over a decade or more. In addition to clinical resources for research, there is not a sufficient number of basic or clinical scientists adequately trained to participate in this research.

Treatment of Chronic Hypertension in Pregnancy. Chronic hypertension during pregnancy is increasing in importance as the proportion of pregnancies to older women increases. This condition is now expected to affect at least 5% of pregnancies annually in the United States. This is a significant public health problem because of the high risk it confers for preeclampsia, and the increased complication rate for mother and fetus when preeclampsia is superimposed on chronic hypertension. In addition, recommendations for treatment of women with chronic hypertension who then become pregnant are based on very little evidence, and have not changed in recent years. The uncertainty includes the utility of non-pharmacological approaches, the choice of drugs, and appropriate blood pressure goals. The preferred approach in the obstetrical community is to substitute alpha-methyldopa, an agent known to be safe in pregnancy, for the antihypertensive therapy prescribed prior to the pregnancy. This decision is due to the fact that alpha-methyldopa is the only hypertensive agent with follow-up safety data in infants. The almost complete absence of data on which to base treatment decisions in this growing group of women, and the difficulty this poses for obstetricians, was emphasized.

RECOMMENDATIONS

In developing recommendations, Working Group members first discussed a number of issues that were viewed as barriers to research progress. In general, although a great deal has been learned about the pathophysiology of preeclampsia and other hypertensive disorders in pregnancy in the past decade, much remains unclear. First, the cardiovascular physiology and placental biology of normal pregnancy are not completely understood, so departures from normal may not be fully appreciated or assessed. Second, in order to advance understanding of the antecedents of preeclampsia, a prospectively collected, well-characterized population is required. Much of the clinical work done to date has relied on retrospective definitions of preeclampsia, with all the inherent difficulties of precision and accuracy this engenders. Third, mechanistic studies linking abnormal implantation to the maternal syndrome of preeclampsia, as well as linking preeclampsia and future cardiovascular risk are lacking. Fourth, the treatment of chronic hypertension in pregnancy, particularly as a potential means of preventing superimposed preeclampsia, has not been evaluated systematically. Finally, there are few obstetrician/gynecologists trained in rigorous clinical research, and even fewer formal training programs.

Specific recommendations were developed from the written materials prepared by Working Group members in advance of the meeting, as well as from the vigorous discussion that occurred at the meeting. After the recommendations were summarized, priorities were assigned using standard techniques for obtaining group consensus. In developing recommendations, the Working Group considered the merits of competing scientific questions, the maturity of hypotheses for clinical testing, and the availability of scientific resources. The research questions deemed to be of the highest priority and the proposed scientific strategies are summarized below.

How does preeclampsia develop, and does it confer future cardiovascular risk?

It is accepted that abnormal implantation of the blastocyst and abnormal placental bed remodeling are prerequisites for preeclampsia, but the mechanistic links between this step and the development of preeclampsia many weeks later are not known. Moreover, little work is currently

being done in this area. **Mechanistic studies should be encouraged, both independently and as part of ongoing or future longitudinal studies to determine the cell biology and physiology that links reduced placental perfusion to the maternal syndrome of preeclampsia.** Studies could focus on basic pathological mechanisms, the natural history of vascular changes in pregnancy, perfusion of the placental vasculature, inflammatory responses, and placental vasculopathy.

Other components of the linkage are the maternal factors that result in a particular woman developing preeclampsia in the setting of reduced placental perfusion. Many such characteristics are also risk factors for later life cardiovascular disease. Fundamental studies of this topic also provide insight into pathophysiological similarities and differences between preeclampsia and later life cardiovascular disease that could be useful in understanding both disorders. Studies exploring mechanisms by which maternal factors predispose to preeclampsia should be encouraged. A related question is whether, once preeclampsia occurs, the woman is at increased risk for future cardiovascular disease. Although this seems to be the case, causality has not been demonstrated. It would be equally plausible to hypothesize that the factors that confer excess risk contribute to the development of preeclampsia in the first place. **This can only be resolved by a prospective observational study in a cohort that will span preconception to postpregnancy.** In this context, markers of cardiovascular risk (e.g., genetic, biochemical, and physiological markers) could be measured serially. A long-term observational study could advance the field significantly by linking outcomes to multiple exposures in temporal sequence. Women with both normal and hypertensive pregnancies would be included, and would be followed from preconception to seven to ten years postpartum, at a minimum. This study could make the important distinction of whether the abnormalities in cardiovascular function that can be identified several years after preeclampsia occurred before the pregnancy and are thus risk factors, or occur only postpartum and thus are residua of the preeclampsia syndrome.

How should chronic hypertension in pregnancy be treated?

Women with chronic hypertension who become pregnant are treated with alpha methyl dopa, based on a single study completed many years ago that had long-term follow up of the offspring to demonstrate fetal safety. Although some antihypertensives such as angiotensin-converting enzyme (ACE) inhibitors are contraindicated in pregnancy, there are a number of alternate antihypertensive agents that should be studied. **A prospective study of antihypertensives in pregnancy should be conducted to evaluate blood pressure control, fetal growth and safety, and genetic variation in response to therapy.**

Will anti-oxidant therapy safely prevent preeclampsia?

Treatment and prevention trials have been disappointing to date. However, several recent studies have suggested causal links between oxidative stress, depletion of vitamin C, low levels of the endogenous vasodilator nitric oxide, and the development of preeclampsia, suggest that there may be a role for anti-oxidant vitamins in the prevention of preeclampsia. **A clinical trial should be undertaken testing the hypothesis that anti-oxidant vitamins can reduce the risk of preeclampsia, reduce maternal and fetal mortality, and increase birthweight.** Such a trial, and all other clinical trials, also should incorporate study of biomarkers and other measures of risk factors and determine predictors and early pathophysiological changes of preeclampsia in low-risk and high-risk populations. A protocol for a similar trial has been developed in the National Institute of Child Health and Human Development's (NICHD) Maternal-Fetal Medicine Units Network and the possibility of a collaborative arrangement of the NHLBI with NICHD in conducting such a trial should be explored. It might be effective to utilize this same resource for a study for the treatment of preexisting hypertension in pregnancy.

How should research capabilities be developed?

Career development programs should be encouraged to enhance the research capabilities of scientists interested in hypertensive disorders of pregnancy. A major goal of career development programs should be to increase the involvement of scientists with diverse research backgrounds and capabilities in the study of hypertensive disorders of pregnancy. A focused effort would improve the skills of individuals working in this area and bring new researchers and skills to bear on the study of hypertensive disorders of pregnancy.

SUMMARY

The hypertensive disorders of pregnancy collectively represent a significant public health problem in the United States and throughout the world. Although great strides have been made in understanding these clinical conditions, a great deal remains to be done. The Working Group's recommendations represent the next steps toward achieving the goal of understanding and preventing complications of hypertension and preeclampsia during pregnancy.

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