The Maternal Phenylketonuria Project: A Summary of Progress and Challenges for the Future

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ABSTRACT. The results of the International Collaborative Study of Maternal phenylketonuria have shown that dietary phenylalanine restriction of women with hyperphenylalaninemia during pregnancy decreases the incidence of mental retardation, microcephaly, congenital heart disease, and intrauterine growth retardation in their offspring. The best results are achieved when treatment is initiated before conception. Psychosocial problems are the most pervasive obstacle to the achievement of optimum dietary treatment. Novel, nondietary approaches to the treatment of maternal phenylketonuria are under development. *Pediatrics* 2003;112:1584-1587; maternal PKU, hyperphenylalaninemia, embryopathy, birth defects, health policy.

ABBREVIATIONS. PKU, phenylketonuria; Phe, phenylalanine; HPA, hyperphenylalaninemia; PAH, phenylalanine hydroxylase; ADHD, attention-deficit/hyperactivity disorder; BH₄, tetrahydrobiopterin.

The proceedings of this conference summarize the results of a multicenter, international, collaborative study, spearheaded by Richard Koch, of unprecedented size, spanning a period of almost 18 years.¹-¹³ During the conference, we heard presentations of papers covering a wide range of subjects directly relevant to our current understanding of phenylketonuria (PKU) in general and maternal PKU in particular. Harvey Levy set the stage with an overview of the history of our awareness of maternal PKU embryopathy, including a review of a seminal article on the problem, which appeared >20 years ago.¹⁴ Besides reviewing data derived from observations on the biology of PKU, we have heard about and discussed various psychological and behavioral observations, social concerns, novel approaches to treatment, and even public policy issues related to the management of the disease.

BIOLOGICAL OBSERVATIONS

The results of the International Maternal PKU Collaborative Study have shown unambiguously that carefully monitored and controlled dietary phenylalanine (Phe) restriction of women with hyperphenylalaninemia (HPA) during pregnancy decreases the incidence of mental retardation, microcephaly, congenital heart disease, and intrauterine growth retardation in their offspring. Moreover, the results of treatment are influenced by the time of initiation of therapy, the quality of the metabolic control achieved and maintained during the pregnancy, the intelligence of the mother, the mother’s general nutrition during pregnancy, and the maternal PAH genotype. The outcome of treatment is best when optimum dietary control of plasma Phe levels is achieved before conception and maintained throughout the pregnancy. When treatment or the achievement of good dietary control of the disease is delayed until 20 weeks of gestation or later, the outcome for the offspring deteriorates rapidly.⁶,¹⁰,¹⁵,¹⁶ The impact of maternal intelligence is complex, not simply as a predictor of the skill of the woman in maintaining good dietary control. Not surprising, the outcome of therapy is better for the offspring of women who maintain good general nutrition throughout pregnancy, assuming good dietary Phe restriction. The offspring of women who have “severe” PAH mutations also tend to have poorer outcomes, in part because of the increased difficulty experienced maintaining good control of plasma Phe levels.

Platt et al¹⁰ summarized and updated earlier reports of the obstetric implications of maternal PKU. No differences were found between women with HPA and control subjects with respect to method of delivery, multiple births, sex of the offspring, or Apgar scores. However, the rate of spontaneous abortion was higher for women with HPA, and their infants were smaller than those of the control women. Widaman reported the results of some elegant statistical analyses of the data derived from the International Maternal PKU Collaborative Study showing that Phe exposure during pregnancy seems to mediate the effects of many of the background variables, such as the severity of the maternal PKU. It also seems to have strong direct as well as indirect effects on cognitive outcomes.

The deleterious effects of maternal HPA are dose related: the better the dietary control, as assessed by serial measurements of plasma Phe levels, the fewer stigmata of maternal PKU embryopathy encountered in the offspring. A great deal of information has emerged relating genotype to phenotype in children with PKU.¹⁷-²¹ To the extent that women with “severe” PAH mutations tend to have poorer outcomes of treatment during pregnancy than women who

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have PKU with other mutations, genotyping has some predictive value. However, it is only 1 variable influencing outcome, and an understanding of the full significance of genotyping for the individual patient requires additional study.

Data were presented from magnetic resonance spectroscopy studies of adults with PKU that may explain, at least in part, why some individuals with the condition seem to tolerate HPA in later life better than others. Although the studies are still small in scale, the results suggest that individuals with PKU differ with respect to the permeability of the blood-brain barrier to Phe and that this may explain the seeming resistance of some adults to the chronic neurotoxic effects of the amino acid.22–26

BEHAVIORAL AND PSYCHOLOGICAL OBSERVATIONS

Elegant longitudinal studies on the behavior of children who are born to mothers with PKU, treated by dietary Phe restriction during pregnancy, showed an increased risk for developmental problems.27 In some respects, the offspring of mothers with PKU resemble children with PKU. Notably, Waisbren reported that maternal PKU children and children who are affected with PKU show significant deficits in executive function. Similarly, both groups of children showed an increased incidence of attention-deficit/hyperactivity disorder (ADHD) that was independent of IQ. However, unlike children who are affected with PKU, who exhibit an inattention type of ADHD, the offspring of mothers with PKU tend to display the full spectrum of behavioral problems associated with ADHD.

SOCIAL ISSUES

Some of the most important observations to issue from the International Maternal PKU Collaborative Study relate to factors that affect compliance with therapy. The data presented by Brown and her colleagues showed that the outcome of the treatment of maternal PKU is affected by a number of nonbiological variables, such as socioeconomic status, the education of the mother, the health belief of the woman on treatment, and the quality of emotional support for the woman, before as well as during pregnancy.28

Following up on previous studies describing psychological social factors that affect compliance with dietary therapy during pregnancy,29,30 Waisbren reported on experience with a pilot project linking women with PKU with “resource mothers” to facilitate compliance with dietary treatment during pregnancy. The results indicated that the psychological and social needs of women with maternal PKU play an important role in the outcome of treatment during pregnancy; however, the needs are complex and require additional study. Brown also identified a number of barriers to successful dietary control of women with PKU during pregnancy. These include access to treatment, the cost of maintaining the therapeutic diet, and the medical expertise available to the patient. The results include no surprises: the same is true of a wide range of chronic, although treatable, illnesses.

PUBLIC POLICY ISSUES

Hanley reported on the observation that some women with untreated PKU are near normal in intelligence. Those who were born before the widespread introduction of newborn screening are often not recognized until they have had 2 or more offspring with maternal PKU embryopathy. He raised the question of whether screening for PKU should be extended to women of childbearing age who are old enough to have escaped detection by newborn screening,31 a question with important implications for the development of screening policies.

We saw how the outcome of the treatment of maternal PKU is influenced by various systemic variables, such as the nature and the amount of resources provided for specialized care. However, other characteristics of the environment in which care is provided have an impact on the results. Sites participating in the International Maternal PKU Collaborative Study in countries or centers with state-supported, unobstructed access to medical care generally had better outcomes.32 Similarly, the results were better when the organization of health care was centralized, with most of the medical care provided, without interruption, by a relatively small group of physicians and other health care professionals with experience and demonstrated interest and expertise in the overall management of PKU. A potent obstacle to access to care in some cases was the absence of comprehensive financial support for special dietary products, medical care, and dietary counseling.

NOVEL APPROACHES TO TREATMENT

The conference included reports on some exciting new developments in the treatment of HPA. Stevens and Trefz reported on experience with the treatment of HPA with tetrahydrobiopterin (BH$_4$).33–35 BH$_4$ is part of the standard treatment of inborn errors of biopterin biosynthesis, which account for only a small percentage of children with persistent HPA. The observation that children have HPA caused by PAH mutations is relatively new. Some children, who are often identifiable by the demonstration of the presence of specific PAH mutations, show a marked increase in dietary Phe tolerance when treated with pharmacologic doses of oral BH$_4$. Most of the responders seem to have atypical PKU, and determination of the role of BH$_4$ supplementation in the overall management of PKU requires additional study.

Other novel nondietary approaches to treatment include oral administration of Phe ammonia lyase, which has been shown to hydrolyze free Phe within the gut to cinnamic acid, which is excreted in the urine. This approach to treatment is still under investigation. Stevens also reported on progress being made in investigation into methods for stabilizing recombinant human PAH to be useful in enzyme replacement therapy of PKU, including by oral administration of the enzyme. Preliminary studies on the possible role of treatment of PKU by administration of large neutral amino acids was reported by Matalon. The results are interesting and certainly merit additional investigation.
type and clinical phenotype in individuals with PKU. Although this is an important predictor, it is only 1 of a myriad of variables that affect the outcome of treatment. Understanding the source and magnitude of other genetic, environmental, behavioral, and social variables that affect the outcome of treatment of maternal PKU (Fig 1) is perhaps the most daunting challenge facing clinical and basic scientists who are involved with efforts to improve the outcome of the treatment of PKU. The achievements of the International Maternal PKU Collaborative Study are truly remarkable. However, in many respects they represent 1 step—a critically important step—in a journey of a thousand miles.

**REFERENCES**


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**Fig 1.** Overview of the domains that interact in the determination of the outcome of treatment of maternal PKU by dietary Phe restriction.

These novel therapeutic alternatives to dietary Phe restriction may make the management of PKU, including maternal PKU, much easier in the future. Determination of their ultimate utility will require the organization of extended, large-scale clinical trials, probably involving >1 PKU treatment center.

**CHALLENGES**

The results of the International Maternal PKU Collaborative Study pose some serious and immediate challenges. One challenge is to work toward the achievement and maintenance of good dietary control of HPA in women with PKU before they become pregnant. This is a formidable undertaking. It requires changes to our system of following individuals with PKU to ensure that they are identified and receive appropriate counseling and support throughout adulthood, especially for women, who are likely to become pregnant. It will also require the identification and correction of a wide range of behavioral, social, and public policy obstacles to access to optimum treatment, whether the treatment is by dietary Phe restriction or some other strategy. The way is clear to achieve some of the changes necessary to improve access to and compliance with treatment. How the necessary resources will be found is a bigger problem. Other proposed solutions to problems of access are almost certainly unrealistically simplistic and require additional sociological and public policy examination for realistic strategies to be developed and implemented.

The development of novel, nondietary approaches to the treatment of PKU represents a longer range and continuing challenge. Experience with the frustrations and dangers inherent in the dietary therapy of maternal PKU and the frequency with which it fails utterly or is only partly successful places added pressure on clinician scientists to develop alternatives to dietary treatment of the condition.

Another continuing and long-range challenge is clarification of the relationship between PAH geno-


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