Historical Background for the Maternal PKU Syndrome

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ABSTRACT. Objective. To provide information on the history of maternal phenylketonuria.
Methods. A review of the literature and personal observations were conducted.
Results. Compilation of sequential information about the development of our understanding of maternal PKU was produced.
Conclusions. The history of maternal PKU reflects continuous additions to our understanding of this teratogenic syndrome. Pediatrics 2003;112:1516–1518; mental retardation, microcephaly, intrauterine growth retardation, congenital heart disease.

ABBREVIATIONS. PKU, phenylketonuria; MPKUCS, Maternal PKU Collaborative Study; MHP, mild hyperphenylalaninemia.

Most discoveries in medicine begin as chance observations, the significance of which is not always recognized even by the observer. So it has been with maternal phenylketonuria (PKU). The first mention of maternal PKU was the observation by Jervis in his classic 1937 survey of PKU that 2 of the phenylketonuric women he was observing had borne children. Jervis was primarily interested in the inheritance pattern of PKU and focused on the fact that at least 2 of the 5 children from these women also had PKU. He mentioned that the 2 with PKU were institutionalized but provided no information about the clinical status of the non-phenylketonuric offspring. Neither he nor others seem to have taken notice of this as examples of maternal PKU.

RECOGNITION OF THE MATERNAL PKU SYNDROME

Almost 20 years was to pass until maternal PKU was noticed as a specific complication of PKU. Such notice first occurred in 1956 during a Ross Pediatric Conference on the causative factors in mental retardation. During the session on the relation of the biochemical abnormality to the development of the mental defect in PKU Charles Dent, a pioneer in the detection of amino acid disorders, mentioned that a woman who had mental retardation and PKU and was observed by Richards had 3 children who had severe retardation despite not having PKU. Dent speculated that the mother’s high blood phenylala-
nine level caused fetal brain damage. Several years later, Richards published additional information about this family.

An appreciation of maternal PKU in its teratogenic entirety, however, began with the specific published studies by Charlton Mabry and his colleagues in Kentucky. In a series of 3 articles, they described 31 children from 7 women with PKU. Of the 22 children who survived infancy and could be studied, 15 had mental retardation and 7 had borderline intelligence. All were nonphenylketonuric. With these publications, it seemed clear that phenylketonuric pregnancies did indeed produce fetal brain damage. That the damage in maternal PKU seemed to be limited to the fetal brain was not surprising because PKU itself was known to affect only the brain.

This effect of maternal PKU on the fetal brain was considered to be limited to mental retardation until 1966, when Fisch et al described microcephaly in 2 maternal PKU offspring. They also mentioned intrauterine growth retardation, thus expanding the features of maternal PKU beyond the brain. Nevertheless, it came as a surprise when a year later, Stevenson and Huntley found a very high frequency of congenital heart disease in maternal PKU offspring. Consequently, these publications led to the view that maternal PKU is a teratogenic syndrome affecting not only the fetal brain but also fetal growth and cardiac development. Moreover, Stevenson and Huntley found that even postnatal growth was impaired in these offspring.

REFINING AN UNDERSTANDING OF THE MATERNAL PKU SYNDROME

For a decade after the publication by Stevenson and Huntley, the articles on maternal PKU consisted of adding more cases and of efforts to call attention to the syndrome. These articles raised concern within the metabolic community that maternal PKU was a potentially serious problem exacerbated by the success of newborn screening and early treatment of PKU. Specifically, it was recognized that preventing mental retardation in PKU would result in relatively large numbers of affected girls’ entering their reproductive years as normal individuals fully capable of bearing children. However, it was also evident that we lacked full knowledge about maternal PKU. Although the teratogenic phenotype seemed to be known, the frequencies of the various features in the offspring were not known, neither was known the relationship of the maternal biochemical severity to the occurrence of the syndrome and to the frequencies of the features. For instance, it was clear that...
there was variability of offspring effects, some offspring reported as even being normal.}

In the late 1970s, I began to think about this gap in our understanding of maternal PKU. I also knew that many centers such as ours had unpublished information about maternal PKU and that this information could significantly close the knowledge gap but might never do so because it was becoming difficult or impossible to publish individual case reports about maternal PKU. Could this information somehow be accessed, and, if so, could it be put together with published data such that a comprehensive view of maternal PKU would emerge? Together with Roger Lenke and with a small contract from the Bureau of Community Health Services of the US Public Health Service made possible by Rudy Hornuth, a questionnaire was developed and sent to metabolic centers throughout the world requesting information about unpublished cases. The information generously sent to us together with an analysis of published cases formed the basis of our special article in the New England Journal of Medicine that appeared in 1980. This compilation established the frequencies of the teratogenic effects relative to the maternal blood phenylalanine level and has provided baseline data for the Maternal PKU Collaborative Study (MPKUCS).

**TREATED MATERNAL PKU**

Soon after the maternal PKU syndrome became recognized, the question of prevention through treatment of the pregnancy arose. It seemed that this might be possible. After all, the brain damage from PKU could be prevented by controlling the blood phenylalanine level. Might such control in the pregnant woman prevent teratogenicity? Allan and Brown were the first to report such a treated pregnancy. Although the diet was administered only during the last 5 months (ie, after 20 weeks’ gestation), the maternal blood phenylalanine level was well controlled (generally <4 mg/dL) and the infant was considered to have better development during the first year of life than his 3 siblings from untreated pregnancies.

The possibility that the fetal damage begins from conception raised the question of whether dietary treatment should begin before conception so that neither the embryo nor the fetus is exposed to the toxic effects of hyperphenylalaninemia. Nielsen and Wamberg addressed this question by instituting treatment before conception. The maternal blood phenylalanine level was controlled at 3 to 8 mg/dL, and the infant was reported to be normal at birth and at 2 weeks of age. Examination of before-conception treatment has been a major focus of the MPKUCS.

**MATERNAL NON-PKU MILD HYPERPHENYLALANINEMIA**

The survey by Lenke and Levy seemed to answer the questions about teratogenicity from maternal PKU, but bias in ascertainment prevented an accurate assessment of maternal non-PKU mild hyperphenylalaninemia (maternal MHP). Unlike maternal PKU, which was usually brought to the attention of the health care community by the mother who was known to the metabolic center or became known through mental deficiency, maternal MHP often came to attention because of an abnormality in the offspring. The question, therefore, was whether the higher-than-normal frequencies of mental retardation and microcephaly in the offspring from maternal MHP pregnancies, although lower than the frequencies in maternal PKU, were a true reflection of teratogenesis in maternal MHP or an artifact of ascertainment. This question was important because almost as many women with hyperphenylalaninemia have MHP as have PKU, given that 30% to 50% of hyperphenylalaninemic infants detected in newborn screening have MHP, not PKU. Moreover, most of these women received little or no dietary treatment in their early years and have been lost to follow-up. Therefore, a substantial tracking and treatment effort would be required if maternal MHP truly represented a teratogenic threat. In Massachusetts, Dr. Waisbren and I had the opportunity to examine this question in an unbiased manner because routine cord blood screening had identified a number of women with MHP. Consequently, we had access to a cohort of offspring from untreated pregnancies in these women, particularly older offspring from pregnancies before the one that led to the cord blood identification. Our study of these offspring led us to conclude that maternal MHP was probably benign.

**MATERNAL PKU COLLABORATIVE STUDY**

The MPKUCS itself represents a historical landmark in maternal PKU as the first large-scale prospective study of treatment and its benefits. The results will set the standard for treatment and will form the model for future studies of maternal PKU and other maternal metabolic disorders.

**REFERENCES**

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