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.1 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 nonphenylketonuric 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.2 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.3

An appreciation of maternal PKU in its teratogenic entirety, however, began with the specific published studies by Charlton Mabry and his colleagues in Kentucky.4–6 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 al7 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 Huntley8 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 Huntley8 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,9 the articles on maternal PKU consisted of adding more cases9 and of efforts to call attention to the syndrome.10 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 off-
spring reported as even being normal.11

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 infor-
mation about maternal PKU and that this informa-
tion 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 some-
how 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 Hor-
muth, a questionnaire was developed and sent to
metabolic centers throughout the world requesting
information about unpublished cases. The informa-
tion 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 1980.12 This compilation established the
frequencies of the teratogenic effects relative to the
maternal blood phenylalanine level and has pro-
vided baseline data for the Maternal PKU Collec-
tive Study (MPKUCS).

TREATED MATERNAL PKU

Soon after the maternal PKU syndrome became
recognized, the question of prevention through treat-
ment 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 preg-
nant woman prevent teratogenicity? Allan and
Brown13 were the first to report such a treated preg-
nancy. 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
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MATERIAL NON-PKU MILD
HYPERPHENYLALANINEMIA

The survey by Lenke and Levy12 seemed to answer
the questions about teratogenicity from 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 retarded-
tion and microcephaly in the offspring from mater-
mal MHP pregnancies, although lower than the fre-
cuencies in maternal PKU, were a true reflection of
teratogenicity in maternal MHP or an artifact of as-
certainment. This question was important because
almost as many women with hyperphenylalanine-
mia have MHP as have PKU, given that 30% to 50%
of hyperphenylalaninemic infants detected in new-
born screening have MHP, not PKU. Moreover, most
of these women received little or no dietary treat-
ment in their early years and have been lost to fol-
low-up. Therefore, a substantial tracking and treat-
ment 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 preg-
nancies 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.15

MATERIAL PKU COLLABORATIVE STUDY

The MPKUCS itself represents a historical land-
mark in maternal PKU as the first large-scale pro-
spective study of treatment and its benefits.16 The
results will set the standard for treatment and will
form the model for future studies of maternal PKU
and other maternal metabolic disorders.

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