
Richard Koch, MD*; William Hanley, MD‡; Harvey Levy, MD§; Kim Matalon, RD, PhD†; Reuben Matalon, MD, PhD¶; Bobbye Rouse, MD∥; Frederick Trefz, MD∥∥; Flemming Güttler, MD, PhD∥∥∥; Colleen Azen, MS*; Larry Platt, MD**; Susan Waissbren, PhDS; Keith Widaman, PhD‡‡; Jiaping Ning, MS*; Eva G. Friedman, BA*; and Felix de la Cruz, MD, MPH§§

ABSTRACT. Objective. The purpose of this report is to review the obstetric medical, psychological, and nutritional aspects and outcome of the women and offspring enrolled in the Maternal Phenylketonuria Study, which was established to assess the efficacy of a phenylalanine (Phe)-restricted diet in preventing the morbidity associated with this disorder.

Methods. A total of 382 women with hyperphenylalaninemia (HPA) were enrolled in the study and completed 572 pregnancies. Outcome measures were analyzed with χ², Fisher exact text, analysis of variance, t test, Wilcoxon nonparametric test, and multiple logistic regression. Outcome measures were stratified according to maternal HPA classification and the time when dietary control was achieved.

Results. Optimal birth outcomes occurred when maternal blood Phe levels between 120 and 360 μmol/L were achieved by 8 to 10 weeks of gestation and maintained throughout pregnancy (trimester averages of 600 μmol/L). Mothers with mild HPA achieved similar birth outcomes as mothers who were in control preconceptionally and those in control by 8 to 10 weeks of pregnancy.

Conclusions. Before conception, counseling and early entrance into a prenatal care program is essential in achieving optimal fetal outcome in women with HPA. The achievement of pre- and periconceptional dietary control with a Phe-restricted diet significantly decreased morbidity in the offspring of women with HPA. Pediatrics 2003;112:1523–1529; pregnancy, maternal phenylketonuria, offspring outcome, phenylalanine-restricted diet.

ABBREVIATIONS. MPKUS, Maternal PKU Collaborative Study; Phe, phenylalanine; HPA, hyperphenylalaninemia; WISC-R, Wechsler Intelligence Scale for Children–Revised; CHD, congenital heart disease; PKU, phenylketonuria.

RESULTS

The background and organization of the Maternal PKU Collaborative Study (MPKUCS) have already been described. The reader is referred to earlier publications for these details, which can be located in earlier publications. Specific questions being addressed by the MPKUCS include the following: 1) What phenylalanine (Phe) level during pregnancy will maintain normal fetal development? 2) Is before-conception Phe restriction necessary? 3) Do mothers with mild hyperphenylalaninemia (HPA) need treatment with a Phe-restricted diet? 4) Is supplementation with tyrosine and various trace elements necessary for normal pregnancy outcome? The purpose of this article is to report on the findings of the subjects who participated in the study.

METHODS

In cooperation with National Institute of Child Health and Human Development and the steering committee of the MPKUCS principal investigators, 13 research hypotheses were developed and are listed elsewhere in the supplement. They required an extension of the project to allow for the collection of Wechsler Intelligence Scale for Children–Revised (WISC-R) data at offspring age of 6 to 7 years. The selection of this age was based on the assumption that it would provide greater credibility than the 4-year data that had been collected with the McCarthy General Cognitive Index.

One of the primary questions posed at the inception of the study related to the efficacy of the Phe-restricted diet on pregnancy outcome. There was widespread disagreement among clinicians concerning this issue. Some were opposed to conception for women with HPA, consequently advising their patients to adopt, and when pregnancy occurred, termination was recommended. Supported by numerous reports on the advantage of before-conception dietary restriction of Phe in improving outcome of fetal development, other clinicians maintained that all pregnancies should be planned with conception occurring only after the establishment of adequate Phe control. However, the degree of Phe restriction has been difficult to ascertain, and it was unclear as to the benefit derived from treating women who were already in their first trimester of pregnancy. In the current collaborative study, the decision was made to accept as study subjects all women who had HPA and were planning a pregnancy or were pregnant, regardless of gestational age. Prospective data thus could be accumulated regarding the efficacy of a Phe-restricted diet not only in women who were treated before conception but also in those whose diet began in either the first, second, or third trimester.

RESULTS

For the significant obstetric data, the reader is referred to 2 articles published by Platt et al. The remainder of this article is devoted to a discussion of the research questions already outlined elsewhere in this supplement.
In regard to research question 1, treatment does reduce fetal morbidity. The gestational age when a Phe-restricted diet was initiated varied among pregnancies, as follows: 148 (25.9%) pregnancies were treated before pregnancy, 263 (46%) of the women with HPA were untreated during the first trimester, 52 (9.1%) were treated in the second trimester, and 4 (0.7%) were treated in the third trimester. Fifty-seven women had mild HPA and were not offered treatment because their blood Phe levels were already within the treatment range. However, clinicians treated 9 women with mild HPA with the Phe-restricted diet at some time during pregnancy. The results in these 2 groups of women with HPA were not statistically different. There is no question that treatment with the Phe-restricted diet during pregnancy is beneficial. When compared with the Lenke-Levy data,4 significant improvement in fetal outcome has occurred. For example, in that study of untreated women with classical phenylketonuria (PKU), microcephaly occurred in 73%, compared with 23% in the present study (Table 1). It is interesting that in the present study, women who achieved metabolic control (120–360 μmol/L) by 10 weeks of pregnancy had offspring with normal cognitive outcome and that only 1 of these infants had congenital heart disease (CHD).

Figure 1 summarizes the effect of treatment on birth length, weight, and head circumference. There is a definite downward trend in all 3 measurements as treatment is delayed during pregnancy. For a summary of the Bayley data at ages 1 and 2 years, the McCarthy scores at 4 and 5 years of age, and the WISC-R at 6 and 7 years of age, the reader is referred to Widaman’s recent analysis based on current data. The issue of factors that contribute to intellectual development in offspring of women with PKU, fat, vitamin, and energy intake also contributed to less-than-optimal outcome.10,13–15 Trace metal defi-

**Table 1.** Effects of Maternal PKU or HPA on Pregnancy Outcome (% Affected)

<table>
<thead>
<tr>
<th>Maternal Off-Diet Phe Levels (μmol/L)</th>
<th>Non-PKU</th>
</tr>
</thead>
<tbody>
<tr>
<td>120–360</td>
<td>901–1199</td>
</tr>
<tr>
<td>Mental retardation, untreated*</td>
<td>92</td>
</tr>
<tr>
<td>MPKUCS</td>
<td>28</td>
</tr>
<tr>
<td>Microcephaly, untreated*</td>
<td>73</td>
</tr>
<tr>
<td>MPKUCS†</td>
<td>23</td>
</tr>
<tr>
<td>CHD, untreated*</td>
<td>12</td>
</tr>
<tr>
<td>MPKUCS</td>
<td>11</td>
</tr>
<tr>
<td>Birth weight ≤2500 g, untreated*</td>
<td>40</td>
</tr>
<tr>
<td>MPKUCS†</td>
<td>21</td>
</tr>
<tr>
<td>Spontaneous abortion, untreated*</td>
<td>24</td>
</tr>
<tr>
<td>MPKUCS</td>
<td>17</td>
</tr>
</tbody>
</table>

* Adapted from Lenke and Levy.4
† Excludes twins.
‡ Not available.

In regard to research question 2, pregnancy outcome in women with HPA is not comparable to that seen in normal women unless strict control is achieved early in pregnancy (see Table 1 and Figs 1 and 6 for comparisons).

The third research question addresses whether pregnancy outcome in women with PKU is related to actual blood Phe levels during pregnancy. Rouse et al9 delineated the multiple problems observed in the offspring born to the women in this study. As a whole, the answer is that treatment does not increase the frequency of spontaneous abortion in maternal PKU, whereas it does reduce microcephaly to 23% and CHD to 7%. Despite this improvement, unusual congenital anomalies, such as tracheoesophageal fistula and esophageal atresia, were observed in 3 offspring. However, if one considers only those women who were treated before conception with good control, microcephaly occurred in only 3.6% of the offspring and in only 5% in offspring of women who were in control with Phe levels between 120 and 600 μmol/L by 10 weeks of pregnancy. Also, CHD was seen in only 3 (2%) children from pregnancies in control with Phe levels <600 μmol/L by 10 weeks of gestation. These numbers are comparable with the 1% to 2% of congenital defects seen in non-PKU pregnancies. Other analyses showed that women with intelligence that is borderline or lower tend to have higher Phe levels and need special support to achieve a normal outcome.

Regarding other factors that influence outcome as posed by research question 4, the data show that increasing gestational age at the time of diet initiation is associated with elevated blood Phe, which is the dominant reason for poor outcome (Figs 5 and 7). Blood tyrosine levels before and during pregnancy were not related to outcome. Phe control was primarily affected by the late initiation of treatment but also by low maternal intelligence. Decreased protein, fat, vitamin, and energy intake also contributed to less-than-optimal outcome.10,13–15
ciencies were not encountered, because of nutritional
guidance.

The fifth research question relating to the impor-
tance of initiating diet before pregnancy with good
control can be answered affirmatively. Data support
erly treatment before and up to 10 weeks of preg-
nancy. The data strongly suggest that the infant who
is born to a well-controlled woman who is treated
before pregnancy is comparable to that of a mother
who gains control by 10 weeks of pregnancy. To our
surprise, the data in Fig 5 also show that offspring IQ
scores at 6 to 7 years of age were better than expected
in pregnancies that were not in control until 10 to 20
weeks of gestation. The mean IQ was 93 on the
WISC-R in this group. This may be related to the fact
that some of these women were ingesting a Phe-
restricted diet before 10 weeks of pregnancy but had
an occasional elevation of blood Phe above 600
µmol/L thereafter. Our definition for the classifica-
tion of 10 to 20 weeks in control was that all levels
after 10 weeks met this criterion. In reconsidering
these data, 19 women with only 1 Phe level >600
µmol/L were reclassified for inclusion in the group
that was in control between 0 and 10 weeks. Even so,
the data still show very similar results, with a mean
IQ of 93 at age 6 to 7 years.

The sixth research question concerning the ade-
quacy of a well-managed Phe-restricted diet to sup-
port normal fetal development can be answered af-
firmatively if proper medical and nutritional
services were provided and if women were compli-
ant. However, the influence of an adequate maternal
IQ should not be ignored. Women with IQs <85
require more intensive services, such as home visits
by skilled nutritionists and nurses with frequent bio-
chemical monitoring, for favorable outcomes.
Without these services, outcome is less favorable.
Güttler et al also documented that the mean IQ of
their offspring is only 79.

The seventh research question about the effect on

Fig 1. Median birth measurement percentiles by week of gestation when Phe was <10 mg/dL.

Fig 2. Relations between maternal background characteristics and child outcomes at 4 and 7 years of age.
fetal outcome of maternal genotype is of great interest. Güttler et al. documented that the women in this study with 2 severe mutations exhibited a mean IQ of only 83 on the WAIS-R Wechsler Adult Intelligence Scale–Revised; those with 1 severe and 1 moderate mutation scored a mean IQ of 84; those with 1 severe and 1 mild mutation scored a mean IQ of 96. Diet discontinuers fared less well in terms of intellectual ability and, in turn, fetal outcome. Mutation severity became detrimental to fetal outcome only when dietary treatment before and during pregnancy was poor. When the quality of care during pregnancy was inadequate, fetal outcome was adversely affected. The longer a woman was treated into the adolescent and teenage years, the higher the mean maternal IQ. In fact, Koch et al. earlier presented data supporting this conclusion. In that report, individuals who had PKU and remained on the diet into adulthood exhibited intellectual abilities comparable to their parents, whereas those who discontinued dietary treatment at 6 years of age scored 10 to 15 points below their parents. In the report by Güttler et al., it should be emphasized that their findings were documented in a cohort of women who had largely discontinued dietary treatment in childhood. Only 21% of the 382 women in the MP-KUCS had maintained treatment into adulthood.

Research question 8 regarding neuropsychological outcome is the subject of extensive investigation by Waisbren and Widaman. The reader is referred to their excellent contributions in this supplement. Figure 5 summarizes the 7-year WISC-R data, demonstrating similar mean IQ scores for offspring of untreated women with mild HPA, women with PKU treated before conception, and those in control by 10 weeks of pregnancy.

Research question 9 focuses attention on the problem of which level of blood Phe control is necessary for optimal fetal outcome. It raises the question of whether the Phe level of 120 to 360 μmol/L is necessary for optimal outcome. This has been a difficult question to answer because the sample size for offspring of pregnancies in control before conception was insufficient for statistical analysis for a number
of the outcome variables. Even so, the WISC-R data at the end of the study included offspring of 18 treated pregnancies with blood Phe levels between 120 and 360 μmol/L before pregnancy. These offspring demonstrated a mean IQ of 105 on the WISC-R at age 6 to 7 years (Fig 7). Offspring of 29 pregnancies with blood Phe control between 360 and 600 μmol/L before pregnancy also had a mean IQ of 105.

Research question 10 attempts to look more closely at the need for establishing Phe control before pregnancy compared with the first 10 weeks of pregnancy. In Fig 7, 14 offspring of mothers who established control in the 120 to 360 μmol/L range between 0 and 10 weeks had a mean IQ of 104, comparable to those with preconception control. The 47 offspring of mothers who attained blood Phe control of 360 to 600 μmol/L between 0 and 10 weeks had a mean IQ of 100, which was lower but not significantly so.

Research question 11 compares the offspring of optimally treated women with PKU with children who were born to mothers in the control group. Sixty-four children who were born to control mothers demonstrated a mean 6- to 7-year WISC-R IQ score of 108, which was not significantly different from the mean IQ of 105 for children who were born to women with optimally controlled blood Phe levels of 120 to 360 μmol/L (Fig 7).

Research question 12 deals with the outcome of children who were born to mothers who were not in control until 10 to 20 weeks of pregnancy. Here again, the results are surprising. Fifty-three women in this group gave birth to children with a mean IQ
on the WISC-R of 93 at 6 to 7 years, which was a higher score than their mothers with a mean IQ of 84 on the Wechsler Adult Intelligence Scale–Revised (Fig 5).

Research question 13 compares the offspring of optimally controlled women with PKU with those with mild HPA. Figure 5 reveals that the offspring of these groups of women are similar in mental ability. The mean WISC-R IQ of the offspring of 47 women who were in control before pregnancy, 62 who were in control before 10 weeks, and 40 who were untreated and had mild HPA were not significantly different.

DISCUSSION

The problem of why most poorly controlled maternal PKU pregnancies are not associated with CHD was not discussed earlier, because it was thought that elevated blood Phe was the cause. CHD occurred in only 7% in the offspring of the MPKUCS and 12% in the Lenke-Levy report. This has been investigated by Matalon et al. Their review was based on the dietary records collected on the 33 cases of CHD in the 372 infants who were born in that study. They found that when poor blood Phe control occurs with inadequate protein, vitamin, and energy intake during the first trimester of pregnancy, CHD was significantly more frequent. The common occurrence of nausea, vomiting, and weight loss in the first trimester are associated with poor nutrition in some pregnancies in which these symptoms are severe. Poor nutrition during the critical period may cause folate and vitamin B12 deficiencies. Nearly all of the infants with CHD exhibited outflow tract defects of the heart. Aortic valvular defects, coarctation of the aorta, hypoplastic left heart syndrome, and patent ductus were the most frequent. These results are consistent with the previous results of Czeizel, suggesting that folic acid deficiency during pregnancy was related to outflow tract defects of the heart.

Analyses suggest that the children who were born to mothers who were in control before pregnancy, those who were born to women who were in control by 8 to 10 weeks of pregnancy, and those who were born to women with mild HPA all have a similar favorable outcome in terms of mean IQ on the WISC-R at 6 to 7 years of age. The rate of CHD in these 3 groups of children was not different from the general population.

CONCLUSION

This study has been unable to prove conclusively that treatment before conception produces offspring that are superior to those who are born to women who establish control during the first 8 to 10 weeks of pregnancy. If there is a difference in these 2 groups, then it could conceivably be attributable to other factors that influence outcome that are as yet unidentified. Furthermore, maternal genotype of the phenylalanine hydroxylase gene becomes important only when the Phe-restricted diet is discontinued early in childhood, resulting in IQ loss to the mother over time. In women with decreased maternal IQ, the present delivery system of medical care in the United States is not adequate to assist such women to achieve a normal outcome. Thus, the major detriment to outcome for children who are born to these women is dependent on normal maternal intelligence and well-treated pregnancies with blood Phe control between 120 and 360 μmol/L. All of these are dependent on the availability of care for their metabolic disorder and high-quality obstetric services in consultation with core staff at recognized metabolic centers. This could be followed by development of a web site of competent consultants and availability of nutrition support staff throughout the world.

ACKNOWLEDGMENTS

This study was supported by National Institutes of Health contract no. N01-HD-2-3148 from the National Institute of Child Health and Human Development (Bethesda, MD) and the National Health Research and Development Program grant 6606-32265 (Ottawa, Ontario, Canada).

Gratitude is expressed to the project staff and to the many health professionals who cooperated in this study, as well as to the...
enrolled women who contributed their time to this long-term effort. The dedicated work by Caroline Guillory and the coordinators of this study in the contributing centers for their outstanding efforts is appreciated: Debby Lobbregt in the Northeast, Barbara Goss in the Midwest, Lois Castiglioni in the Southeast, and Elizabeth Wenz in the western part of the United States, as well as Wanda Schoonheyt in Toronto, Ontario, Canada, and Sanja Cipcic-Schmidt in Heidelberg, Germany.

REFERENCES
Richard Koch, William Hanley, Harvey Levy, Kim Matalon, Reuben Matalon, Bobbye Rouse, Frederick Trefz, Flemming Güttler, Colleen Azen, Larry Platt, Susan Waisbren, Keith Widaman, Jiaping Ning, Eva G. Friedman and Felix de la Cruz

Pediatrics 2003;112;1523

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/112/Supplement_4/1523

References
This article cites 11 articles, 1 of which you can access for free at:
http://pediatrics.aappublications.org/content/112/Supplement_4/1523.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Genetics
http://classic.pediatrics.aappublications.org/cgi/collection/genetics_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2003 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .
Richard Koch, William Hanley, Harvey Levy, Kim Matalon, Reuben Matalon, Bobbye Rouse, Frederick Trefz, Flemming Güttler, Colleen Azen, Larry Platt, Susan Waisbren, Keith Widaman, Jiaping Ning, Eva G. Friedman and Felix de la Cruz

*Pediatrics* 2003;112;1523

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/112/Supplement_4/1523